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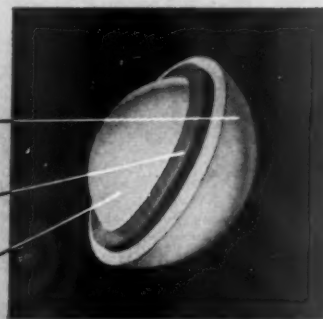
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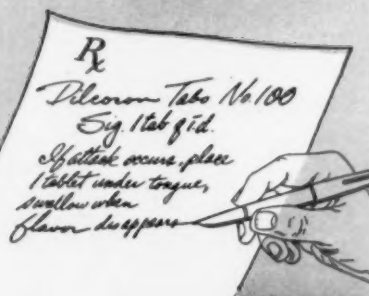
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The American Journal of Medicine

Vol. XXIV FEBRUARY, 1958 No. 2

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Clinical Studies

The Vascular Status of a Heterogeneous Group of Patients with Hypertension, with Particular Emphasis on Renal Function

JOHN H. MOYER, CHARLES HEIDER, KEITH PEVEY AND RALPH V. FORD 164

The Effect of Treatment on the Vascular Deterioration Associated with Hypertension, with Particular Emphasis on Renal Function

JOHN H. MOYER, CHARLES HEIDER, KEITH PEVEY AND RALPH V. FORD 177

This large-scale, long-term study of the progressive deterioration of glomerular filtration rate and renal blood flow in essential hypertension, and the deterrent effect thereon of antihypertensive therapy, deserves careful consideration. The first paper gives an account of the natural history of untreated essential hypertension, with special reference to renal function. It substantiates previous renal clearance studies but the serial determinations bring out more clearly the sometimes alarming rapidity of renal deterioration when hypertension is marked. The second paper contrasts the unremitting downward course of untreated hypertensive patients with the usually arrested progression of renal vascular deterioration in adequately treated patients with severe or moderately severe hypertension. There was a substantial reduction in morbidity and mortality. The authors advance these results as a solid argument for early and vigorous antihypertensive treatment of hypertensive vascular disease. Further work along these lines is needed.

The Paradox of Right Ventricular Enlargement in Mitral Insufficiency

LAMBERTO BENTIVOGLIO, JOSEPH F. URICCHIO AND WILLIAM LIKOFF 193

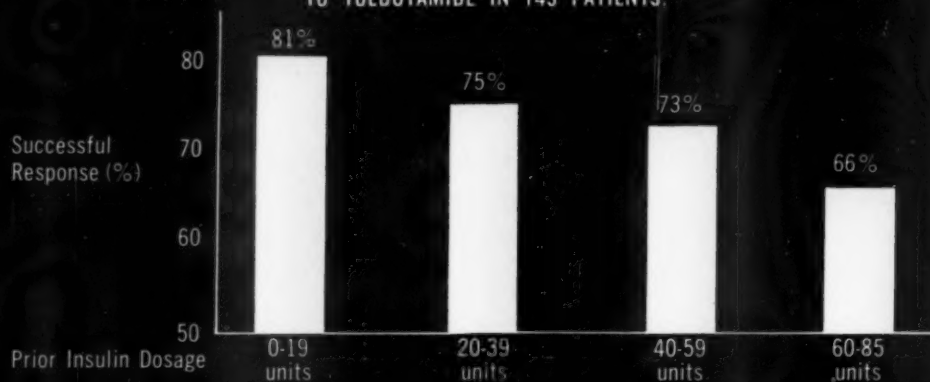
The authors deal with the occasional occurrence of predominant right ventricular enlargement in patients who have mitral insufficiency without mitral stenosis demonstrable at cardiac catheterization or by direct examination at surgical exploration or at autopsy. This apparent hemodynamic paradox is reasonably referred to decrease in the usual stretch, in such cases, of the left atrium in response to its augmented volume load. In consequence, disproportionate rises in pressure are transmitted to the pulmonary circuit and cause marked pulmonary hypertension, structural changes in the pulmonary vasculature and right ventricular enlargement. All this may occur before the left ventricle fails or even markedly hypertrophies.

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AN AMES CLINIQUICK

CLINICAL BRIEFS FOR MODERN PRACTICE

CORRELATION OF PRIOR INSULIN DOSAGE WITH SUCCESSFUL RESPONSE TO TOLBUTAMIDE IN 143 PATIENTS



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Localization of Left-to-Right Cardiac Shunts by Dye-Dilution Curves Following Injection into the Left Side of the Heart and into the Aorta

EUGENE BRAUNWALD, HERBERT L. TANENBAUM AND ANDREW G. MORROW 203

This paper describes an ingenious use of dye-dilution curves to localize left-to-right cardiac shunts more precisely. The dye is injected into the catheterized left side of the heart or into the aorta, and the indicator dilution curve is recorded from a systemic artery or from the ear. Several case reports are cited to illustrate how the method served to advantage in defining structural defects amenable to correction by surgery.

Isorhythmic Dissociation. Atrioventricular Dissociation with Synchronization

ADALBERT F. SCHUBART, HENRY J. L. MARRIOTT AND RALPH J. GORTEN 209

It is recognized that the independence of atria and ventricles in A-V dissociation and complete A-V block is not always absolute. In this study five cases of A-V dissociation are presented in which there was some tendency for the atria and ventricles to contract synchronously or almost synchronously—what has been termed accrochage. Possible mechanical and electrical mechanisms that are operative in this phenomenon are discussed, and criteria for recognizing it, since it may occur more frequently than supposed, are proposed.

The Effect of Salicylates upon the Ventilatory Response to Carbon Dioxide in Patients with Pulmonary Emphysema and Hypercapnia

PHILIP SAMET, ANNA ROSENTHAL AND WILLIAM H. BERNSTEIN 215

Salicylate therapy in patients with obstructive emphysema and carbon dioxide retention failed to improve the ventilatory response to inhaled carbon dioxide or to inhibit the depression of ventilation following inhalation of gas mixtures containing a high percentage of oxygen. Contrary to previous reports, salicylates did not increase the sensitivity of the respiratory center to the normal chemical stimuli. It is suggested that the increase in ventilation produced by salicylate therapy is secondary to the metabolic effects of the drug, and that the depressed ventilatory response to inhaled carbon dioxide in patients with pulmonary emphysema is not reversed by such salicylate therapy.

Some Effects of Change in Position on Pulmonary Function in Bronchial Asthma

ALAN L. MICHELSON AND FRANCIS C. LOWELL 225

This study was aimed at explaining why patients with bronchial asthma are apt to have increased difficulty in breathing upon retiring at night. One explanation revolves upon the normal decline in vital capacity with recumbency. However, this was not observed in one-third of the asthmatic subjects tested, from which it is concluded that other factors, not here defined, must play a role.

Hypercalcemic Crisis Due to Hyperparathyroidism

WILLIAM C. THOMAS, JR., JOHN G. WISWELL, THOMAS B. CONNOR
AND JOHN E. HOWARD 229

The acute manifestations of marked hypercalcemia are now more generally appreciated but still offer difficulties in differential diagnosis. Failure to recognize the syndrome is particularly un-

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fortunate in "acute" hyperparathyroidism, since this is remediable. These points are made and illustrated by relevant cases in the present study, which admirably summarizes present knowledge of this subject.

Phosphate Clearance in the Diagnosis of Parathyroid Dysfunction

LAURENCE H. KYLE, MARCUS SCHAAF AND JOHN J. CANARY 240

Prevailing views of the role of the parathyroid glands in the regulation of the renal excretion of inorganic phosphate in man have been much confused by experiments which, because of variation in experimental conditions, parathyroid extracts employed, species differences, and other important factors, give results not simply translatable to human physiology or pathology. There is even some doubt that the parathyroid hormone(s) has any effect on tubular reabsorption of phosphate! The experiments of nature—hyper- and hypoparathyroidism—are much simpler and more direct. As indicated in this paper, which does much to clear the air, such a regulatory role can be unequivocally demonstrated and can be applied to diagnosis in hyper- or hypoparathyroid states, if various complicating factors are properly taken into account. The authors point out certain advantages, in this connection, of determination of the phosphate clearance as compared with estimation of the percentage of filtered phosphate load which is reabsorbed by the tubules.

Review

Clinical and Histologic Spectrum of the Nephrotic Syndrome

LEONARD B. BERMAN AND GEORGE E. SCHREINER 249

Debate on the various aspects of the nephrotic syndrome continues to be spirited, as this discussion attests. The authors attempt to correlate morphologic changes in the kidneys, as observed by microscopic examination chiefly of sections obtained by aspiration biopsy of the kidney, with the clinical diagnosis and course. These correlations lead to a new etiologic classification of the nephrotic syndrome (which presumably is not intended to be definitive), a new definition of the nephrotic syndrome, and a number of stimulating new points of view, none of startling novelty. The whole makes for an interesting and well rounded discussion. As the authors imply, one should not lose sight of the fact that probably the most significant functional defects of the glomeruli and tubules are not visible under the microscope, even the electron microscope.

Seminar on Liver Disease

Chronic Idiopathic Jaundice. A Review of Fifty Cases I. N. DUBIN 268

Dr. Dubin has brought together, in one authoritative review, the available information concerning a newly recognized and particularly intriguing liver disorder, more commonly known as Dubin-Johnson's disease. The indications are that, like Gilbert's disease, this disorder reflects an inborn error of metabolism, but one in which the defect involves hepatic excretory mechanisms. Clinically, confusion with cholelithiasis is apt to occur because of the recurrent jaundice, right upper quadrant pain, dark urine and pale stools; or familial non-hemolytic jaundice may be simulated by the early onset and chronicity of mild jaundice and the familial tendency. However, as this review makes

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clear, diagnosis by clinical and laboratory differentiation is possible, with confirmation by liver biopsy. It is evident that the complete clinician should be familiar with the manifestations of this interesting disease.

Clinico-pathologic Conference

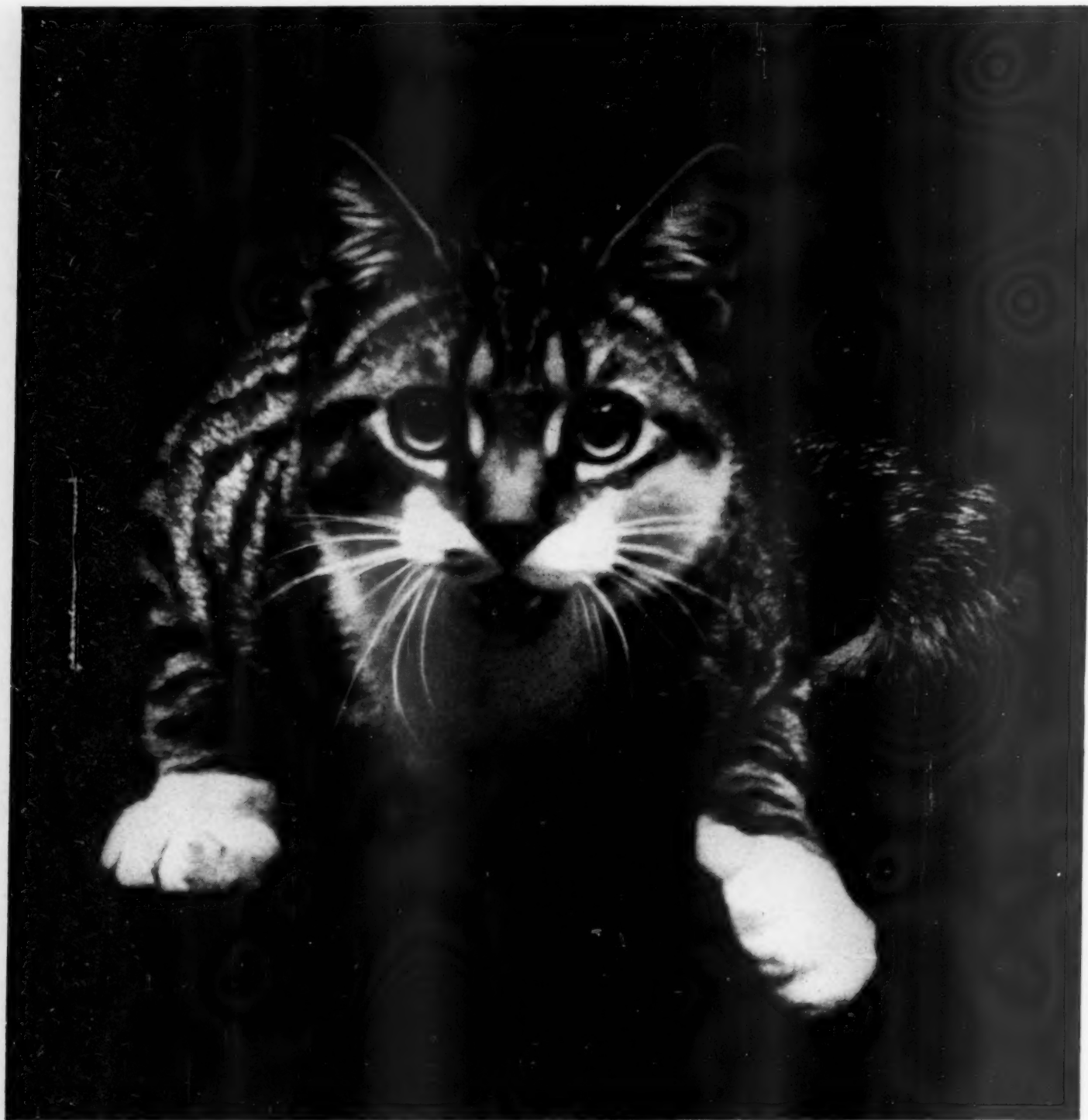
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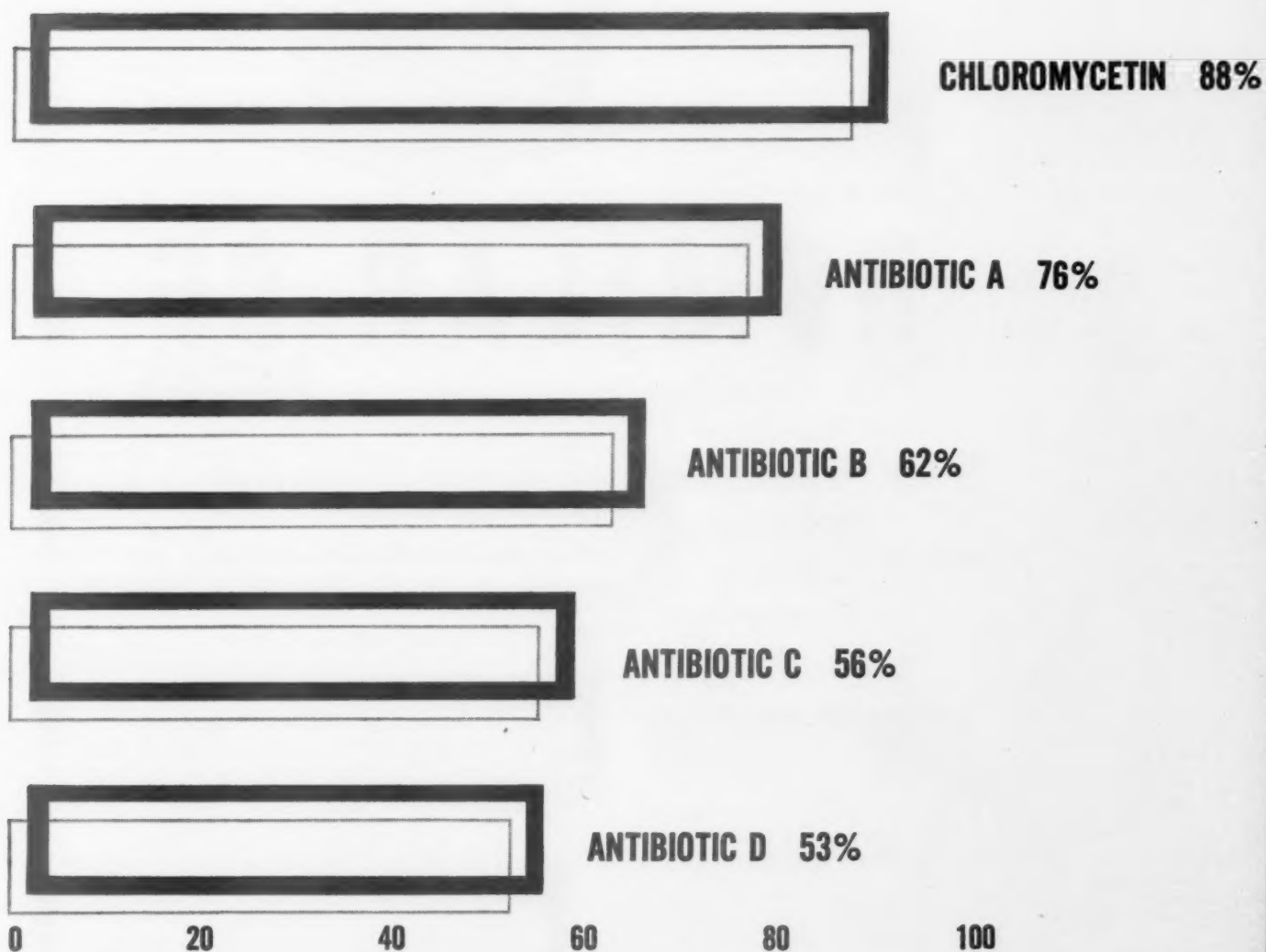
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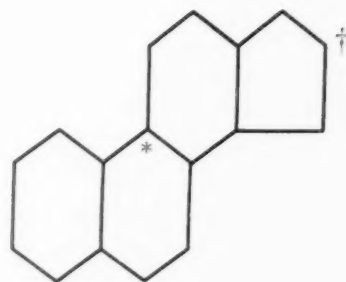


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Kidney function

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Sodium and water

ARISTOCORT produced an increase of 230 per cent of water diuresis and 145 per cent sodium excretion when compared to control animals.¹ Metabolic balance studies in man revealed an average negative sodium balance of 0.8 Gm. per day throughout a 12-day period on a dosage of 30 mg. per day.² Additional balance studies showed actual sodium loss when ARISTOCORT was given in doses of 12 mg. daily.³ Other investigators observed significant losses of sodium and water during balance studies and that those patients with edema from some older corticosteroids lost it when transferred to ARISTOCORT.^{4,5} In two studies of various rheumatic disorders (194 cases) on prolonged treatment, sodium and water retention was not observed in a single case.^{6,7}

Potassium and chlorides

There was no active excretion of potassium or chloride ions in animals given maintenance doses of ARISTOCORT 25 times that found to be clinically effective.¹ Potassium balance studies in humans^{2,3} revealed that negative balance did not occur even with doses somewhat higher than those employed for prolonged therapy in rheumatoid arthritis. Hypokalemia, hyperkalemia or hypochloremia did not occur, when tested, in 194 patients with rheumatoid arthritis treated for up to ten and one-half months.^{6,7}

Calcium and phosphorus

Phosphate excretion in animals¹ was not changed from normal even with amounts 25 times greater (by body weight) than those known to be clinically effective. Human metabolic balance studies³ demonstrated that no change in calcium excretion occurred on dosages usually employed clinically when the compound is administered for its anti-inflammatory effect. Even at a dosage level twice this, slight negative balance appeared only during a short period.

Protein and nitrogen balance

Positive nitrogen balance was maintained during a human metabolic study on maintenance dosage of 12 mg. per day.³ At dosages two to three times normal levels, positive balance was maintained except for occasional short periods in metabolic studies of several weeks' duration.^{2,3}

There was always a tendency for normalization of the A/G ratio and elevation of blood albumin when ARISTOCORT was used in treating the nephrotic syndrome.⁸



Liver glycogen deposition and inflammatory processes

An intimate correlation exists between the ability of a corticosteroid to cause deposition of glycogen in the liver and its capacity to ameliorate inflammatory processes.

In animal liver glycogen studies, relative potencies of ARISTOCORT over cortisone of up to 40 to 1 have been observed. Compared to ARISTOCORT, five to 12 times the amount of prednisone is required to produce varying but equal amounts of glycogen deposition in the liver.¹

Most patients show normal fasting blood sugars on ARISTOCORT. Diabetic patients on ARISTOCORT may require increased insulin dosage, and occasional latent diabetics may develop the overt disease.

Anti-inflammatory potency of ARISTOCORT was determined by both the asbestos pellet¹ and cottonball⁹ tests. It was found to be nine to 10 times more effective than hydrocortisone in this respect.

Gastric acidity and pepsin

The precise mode of ulcerogenesis during treatment with corticosteroids is not known. There is much experimental evidence for believing this may be related to the tendency of these agents to increase gastric pepsin and acidity—and this cannot be abolished by vagotomy, anticholinergic drugs or gastric antral resection.¹⁰ Clinical studies¹¹ of patients on ARISTOCORT revealed that uropepsin excretion is not elevated. Further, their basal acidity and gastric response to histamine stimulation were within normal limits.

Central nervous system

The tendency of corticosteroids to produce euphoria, nervousness, mental instability, occasional convulsions and psychosis is well known.¹² The mechanism underlying these disturbances is not well understood.

ARISTOCORT, on the contrary, does not produce a false sense of well being, insomnia or tension except in rare instances. In the treatment of 824 patients, for up to one year, not a single case of psychosis has been produced. In general, it appears to maintain psychic equilibrium without producing cerebral stimulation or depression.

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The Promise of Aristocort

in Reduction of Side Effects

○ It is axiomatic to affirm that the undesirable collateral hormone effects of corticosteroids increase in frequency and severity the higher the dosage and the longer used.

It has also become well recognized that the most serious of the major side effects from long-term corticosteroid treatment are peptic ulcers, osteoporosis with fracture, drug psychosis and euphoria, and sodium and water retention leading often to general tissue edema and hypertension.

It is significant that of the close to 400 patients on the lower dosage schedules found effective in bronchial asthma and dermatologic conditions, only 1 case of peptic ulceration has developed. No other of the above side effects have been observed even though ARISTOCORT was administered continuously to them for periods as long as one year.

The treatment of rheumatoid arthritis with steroids appears to result in the highest incidence of side effects. For this reason, the side effects associated with ARISTOCORT therapy in 292 patients with rheumatoid arthritis are below compared to the reported incidence of those from prednisone and prednisolone.

Peptic Ulcer

The most recent study available on the incidence of peptic ulceration in patients with rheumatoid arthritis on long-term prednisone therapy reported 12 ulcers in 49 cases (24 per cent).¹ Lowest incidence of 6.5 per cent has been recorded in a group of patients on this drug for six to nine months.² Four of six ulcers, in another series of 39 patients on prednisone,³ appeared in less than three months of therapy.

The occurrence of peptic ulcer in 292 patients with rheumatoid arthritis treated continuously for up to one year with ARISTOCORT is approximately 1 per cent (2 of the 3 occurred in patients transferred from prednisone). In the remaining 532 cases recently

analyzed, only one ulcer has been discovered in a patient who apparently had no ulcer when he was changed from another steroid.

Osteoporosis and Compression Fractures

The incidence of compressed fractures of vertebrae—and to a lesser extent in other bones—is high in patients on prolonged therapy with all previous corticosteroids.⁴ One group of 49 patients¹ on long-term prednisone treatment experienced nine vertebral fractures (18 per cent); another series of 39 developed eight fractures (20 per cent),³ four to 15 months after the beginning of steroid administration.

The occurrence of osteoporosis with compression fracture in 292 patients with rheumatoid arthritis treated continuously for up to one year with ARISTOCORT is 0.33 per cent (1 case⁵). Although these results are encouraging, determination of the true incidence of osteoporosis will have to await the passage of more time.

Euphoria and Psychosis

The euphoria so commonly produced by all previous corticosteroids has seemed a most desirable attribute to patients. In penalty, however, they have often later to pay for this by mental disturbances, varying from mild and transitory to severe depression and psychosis,⁴ and toxic syndromes producing even convulsions and death.⁶

Since the onset of these complications is not directly related to duration of steroid administration,⁷ the fact that not one case of psychosis occurred in 824 patients treated with ARISTOCORT, is most encouraging.

Sodium Retention—Hypertension—Potassium Depletion

When 17 patients were changed from prednisone to ARISTOCORT, 11 rapidly lost weight although only one had had visible edema.⁸ Sodium and water retention, hypokalemia or hyperkalemia and steroid hypertension did not appear in 194 rheumatoid arthritis patients treated with ARISTOCORT.^{5,9}

The interrelation between blood and body sodium, and steroid hypertension has long been generally appreciated.^{10,11} Except in rare instances, or when unusually high doses are used (e.g., leukemia), the problem of edema and hypertension caused by sodium and water retention, has been eliminated with ARISTOCORT.

Minor Side Effects

Collateral hormonal effects of less serious consequence occurred with approximately the same frequency as with the older corticosteroids.⁵ These include erythema, easy bruising, acne, hypertrichosis, hot flashes and vertigo. Several investigators have reported symptoms not previously described as occurring with corticosteroid therapy, e.g., headaches, light-headedness, tiredness, sleepiness and occasional weakness.

Moon facies and buffalo humping have been seen in some patients on ARISTOCORT. However, ARISTOCORT therapy, in many instances, resulted in diminution of "Cushingoid" signs induced by prior therapy. Where this occurs, it may be related to reduced dosage on which patients can be maintained.

Reduction of dosage by one-third to one-half

In a double-blind study of comparative dosage in patients with rheumatoid arthritis,¹² 70 per cent of the cases were as well controlled on a dose of ARISTOCORT one-half that of prednisone. A general recommendation can be made that ARISTOCORT be used in doses two-thirds that of prednisone or prednisolone in the treatment of rheumatoid arthritis. There are individual variations, however, and each patient should be carefully titrated to produce the desired amount of disease suppression.

Comparative studies, of patients changed from prednisone, indicate reduced dosage of ARISTOCORT in bronchial asthma and allergic rhinitis (33 per cent),⁸ and in inflammatory and allergic skin diseases (33-50 per cent).^{13,14}

General Precautions and Contraindications

Administration of ARISTOCORT has resulted in a lower incidence of the major serious side effects, and in fewer of the troublesome minor side effects known to occur with all previously available corticosteroids. However, since it is a highly potent glucocorticoid, with profound metabolic effects, all traditional contraindications to corticosteroid therapy should be observed.

No precautions are necessary in regard to dietary restriction of sodium or supplementation with potassium.

Since ARISTOCORT has less of the traditional side effects, the appearance of sodium and water retention, potassium depletion, or steroid hypertension cannot be used as signs of overdosage. As a rule patients will lose some weight during the first few days of treatment as a result of urinary output, but then the weight levels off.

Patients do not develop the abnormally voracious appetite common to previous corticosteroid administration. In fact, some patients experienced anorexia, and it is advisable to inform patients of this and to recommend they maintain a normal intake of food, with emphasis on liberal protein intake.

While precipitation of diabetes, peptic ulcer, osteoporosis, and psychosis can be expected to appear rarely from ARISTOCORT, they must be searched for periodically in patients on long-term steroid therapy.

Traditional precautions should be observed in gradually discontinuing therapy, in meeting the increased stress of operation, injury and shock, and in the development of intercurrent infection.

There is one overriding principle to be observed in the treatment of any disease with ARISTOCORT. *The amount of the drug used should be carefully titrated to find the smallest possible dose which will suppress symptoms.*

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The Promise of Aristocort

in Rheumatoid Arthritis

○ ARISTOCORT therapy has been intensely and extensively studied for periods up to one year on 292 patients with rheumatoid arthritis.

Significant is the fact that most patients were severe arthritics, transferred to ARISTOCORT from other corticosteroids because satisfactory remission had not been attained, or because the seriousness of collateral hormonal effects had made discontinuance desirable.

Results of treatment

Freyberg and associates¹ treated 89 patients with rheumatoid arthritis (A. R. A. Class II or III and Stage II or III). Of these, 51 were on ARISTOCORT therapy from three to over 10 months. In all but a few patients, satisfactory suppression of rheumatoid activity was obtained with 10 mg. per day. Thirteen were controlled on 6 mg. or less a day, and for periods to 180 days. The investigators reported therapeutic effect in most cases to be A. R. A. Grade II (impressive) and that marked reduction in sedimentation rates occurred.

Another interesting observation in this study: Of the 89 patients treated, 12 had active ulcers, developed from prior steroid therapy. *In six patients, the ulcers healed while on doses of ARISTOCORT sufficient to control arthritic symptoms.*

Hartung² treated 67 cases of rheumatoid arthritis for up to 10 months. He found the optimum maintenance dose to be 11 mg. per day. Nineteen of these patients were treated for six to 10 months with an "excellent" therapeutic response.

Dosage and course of therapy

The initial dosage range recommended is 14 to 20 mg. per day—depending on the severity and acuteness of signs and symptoms. Dosage is divided into four parts and given with meals and at bedtime. Anti-rheumatic effect may be evident as early as eight hours, and full response often obtained within 24 hours. This dosage schedule should be continued for two or three days, or until all acute manifestations of the disease have subsided, whichever is later.

The maintenance level is arrived at by reduction of the total daily dosage in decrements of 2 mg. every three days. The range of maintenance therapy has been found to be from 2 mg. to 15 mg. per day—with only a very occasional patient requiring as much as 20 mg. per day. Patients requiring more than this should not be long continued on steroid therapy.

The aim of corticosteroid therapy in rheumatoid arthritis is to suppress the disease only to the stage which will enable the patient to carry out the required activities of normal living or to obtain reasonable comfort. The maintenance dose of ARISTOCORT to achieve this end is arrived at while making full use of all other established methods of controlling the disease.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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The Promise of Aristocort

in Respiratory Allergies

○ About 200 patients with respiratory allergies have been treated with ARISTOCORT for continuous periods up to eight months.

Results of treatment

Sherwood and Cooke^{1,2} gave ARISTOCORT to 42 patients with bronchial asthma and allergic rhinitis. Average dose needed to control the asthmatic group was approximately 6 mg. per day (range, 2 to 14 mg.). Results, which were called "good to excellent" in all but four, were achieved on one-third less than similarly effective doses of prednisone or prednisolone.

The investigators noted other major improvements in ARISTOCORT therapy over the older steroids. There was no increase in blood pressure in any patient: *on the contrary, in 12 patients, there was reduction of pressure when they were transferred to ARISTOCORT.* One patient had required auxiliary antihypertensive drug therapy; over a nine-week period on ARISTOCORT, the pressure gradually fell from 206/100 to 136/79. In another case, the pressure slowly dropped from 205/105 to 154/86.

The number of cases in which these investigators tried ARISTOCORT in allergic rhinitis was not large enough to provide significant averages. However, the range of effective therapy was from 2 to 6 mg. per day. These strikingly low daily doses resulted in control of all signs and symptoms.

Schwartz³ treated 30 patients with chronic, intractable bronchial asthma. At an average daily dose of 7 mg., he reported "good to excellent" results in all but one. Spies,⁴ Barach⁵ and Segal,⁶ reported similar results at average daily maintenance doses of 4 to 10 mg. of ARISTOCORT.

Dosage and course of therapy

The initial dosage range recommended is 8 to 14 mg. of ARISTOCORT daily. Although a rare, very severe case may require more than this on the first day of therapy, these dosages will usually result in prompt alleviation of dyspnea, wheezing and cyanosis. Patients are soon able to carry out a normal span of daily activity.

The maintenance level is arrived at by reduction of the total daily dose every three days in decrements of 2 mg.; in the over-all series, the average daily dose for bronchial asthma is approximately 8 to 10 mg. and for allergic rhinitis, 2 to 6 mg. per day. All total daily doses should be divided into four parts and given with meals and at bedtime. As in every condition where corticosteroids are employed, each patient's treatment should be individualized and the maintenance arrived at by careful titration against signs and symptoms of disease.

Patients with chronic bronchial asthma may require steroid therapy for several months. And since asthma may be associated with cardiac disease, especially in the older age groups, ARISTOCORT is particularly useful because of its ability to cause excretion of sodium and water.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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The Promise of Aristocort

in Nephrotic Syndrome

- ◊ Fourteen patients with the nephrotic syndrome have been treated with ARISTOCORT for continuous periods of up to six weeks.

Results of treatment

Hellman and associates^{1,2} noted that ARISTOCORT, because of its favorable electrolyte effects, may well be the most desirable steroid to date in treatment of the nephrotic syndrome. However, thus far its use has been reported in only 14 children, of whom 8 had a complete diuresis and disappearance of all abnormal chemical findings. Four of the patients had diuresis, but continued to show some abnormal chemical findings, while two patients with signs of chronic renal disease failed to respond.

Dosage and course of therapy

In order to produce maximal response, 20 mg. should be given daily until diuresis occurs. The dose should then be decreased gradually and maintained around 10 mg. a day. After the patient has been in remission for some time, it may be advisable to diminish the dose gradually and discontinue ARISTOCORT.

in Pulmonary Emphysema and Fibrosis

- ◊ Eleven patients with pulmonary emphysema and/or fibrosis were treated with ARISTOCORT for continuous periods of over two months.

Results of treatment

Only small series of cases observed by Barach,³ Segal,⁴ and Cooke,⁵ are available. Barach treated patients who were not adequately controlled by prednisone, with the same dose of ARISTOCORT with significant improvement.

Dosage and course of therapy

The initial suppressive dose range recommended is 10-14 mg. daily. Frequently, there is a prompt decrease in cyanosis and dyspnea, with increase in vital capacity.

The average maintenance dose level was 8 mg. a day. If it is desired to maintain a patient on continuous therapy for some months, dosages as low as 2 mg. a day have been successful. All decreases in dosage should be gradual and at a rate of 2 mg. decrements in total daily amount, every two to four days. The daily dosage is divided into four parts and given with meals and at bedtime.



in Neoplastic Diseases

○ Forty-four children and adults have been given ARISTOCORT for palliative treatment of acute leukemia, chronic lymphatic leukemia, lymphosarcoma, lympholeukosarcoma and Hodgkin's disease.

Results of treatment

Farber⁶ has treated 22 children with acute leukemia for an average of three weeks. Of the 17 observed long enough to judge the efficacy of the medication, he rated five as excellent, three as good, two as fair and seven as poor responses.

Hellman and associates⁷ gave ARISTOCORT to a group of patients with the various lymphomas in doses of 40 to 50 mg. a day—occasionally up to 100 milligrams. Treatment was continued in some cases for 17 weeks. Response was classified as good for the palliative purposes for which the drug was given.

Dosage and course of therapy

Massive initial suppressive doses of 40 to 50 mg. per day in children (1 mg./kg./day) and up to 100 mg. a day in adults have been administered.

Responses to any specific dosage in these conditions vary so widely that only a general dosage range can be indicated. Treatment

must be individualized; rate of reduction in dosage and determination of maintenance levels cannot be categorized.

Miscellaneous

Patients with various other diseases have been treated by several clinical investigators. These include patients with osteoarthritis, acute bursitis, rheumatic fever, spondylitis, other "collagen-vascular" diseases (dermatomyositis, etc.), thrombocytopenic purpura, chronic eosinophilia, hemolytic anemia, diuretic-resistant congestive heart failures, and adrenogenital syndrome.

There have not been sufficient patients in any of the above categories to permit definitive treatment schedules to be finally established for ARISTOCORT. Additional studies are now in progress and physicians desiring information on any of these diseases are requested to write to Lederle Laboratories, Pearl River, New York for available data.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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Lederle

The Promise of Aristocort

in Inflammatory and Allergic Skin Diseases

Over 200 patients with allergic and inflammatory skin diseases (including psoriasis, atopic dermatitis, exfoliative dermatitis, pemphigus, dermatitis herpetiformis, eczematoid dermatitis, contact dermatitis and angioneurotic edema) have been treated continuously with ARISTOCORT for periods of up to eight months.

Results of treatment

Rein and associates¹ treated 26 patients with severe dermatitis. Twenty-four had been on prednisone when changed to ARISTOCORT. While some had found satisfactory symptomatic relief, others had also developed side effects—moon face, buffalo hump, increased appetite with excessive weight increases and gastro-intestinal disturbances.

These investigators determined the equivalent dosage of ARISTOCORT to be approximately two-thirds that required to control symptoms on the previous corticosteroid. Thirteen of the 26, who had developed moon face, noted either an actual decrease or no further increase when transferred to ARISTOCORT. In addition: *Voracious appetites disappeared, with loss of weight in 11 patients; there was no elevation in blood pressure, and no necessity to restrict sodium or administer supplemental potassium.* Sherwood and Cooke,² and Shelley and Pillsbury³ obtained similar results in allied disorders, and also noted absence of serious side effects.

Hollander⁴ first observed that ARISTOCORT appears to have striking affinity for the skin and great activity in controlling such diseases as psoriasis, for which other corticosteroids have been indifferently effective. Shelley and Pillsbury,³ in 50 cases of acute extending psoriasis found that 90 per cent were significantly improved.

Dosage and course of therapy

The recommended initial suppressive dose range is 14 to 20 mg. per day. In very severe cases, temporary dosages up to 32 mg. a day

have been successfully employed. Once lesions are suppressed, gradually reduce dose to the maintenance level—which may be as low as 2 mg. per day.

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in Disseminated Lupus Erythematosus

Forty patients with disseminated lupus erythematosus were treated with ARISTOCORT for continuous periods of up to nine months.

Results of treatment

Patients have responded very promisingly to therapy. Dubois¹ has had the largest single experience (28 cases) with ARISTOCORT in the treatment of this disease. He reported 25 of the 28 responded favorably.

Freyberg,² Hartung,³ Hollander,⁴ Spies,⁵ and Segal,⁶ each in smaller series of cases, reported similarly good therapeutic responses with absence of serious side effects.

Dosage and course of therapy

The initial suppressive dose recommended is 20-30 mg. daily. Once the desired effect is achieved, the dose should be reduced gradually to maintenance levels (3 to 18 mg. per day).

In severely ill patients large doses may be required for several days in order to preserve life. Even on these large doses, edema and sodium retention have not occurred.

ARISTOCORT is available in 2 mg. scored tablets (pink); 4 mg. scored tablets (white). Bottles of 30.

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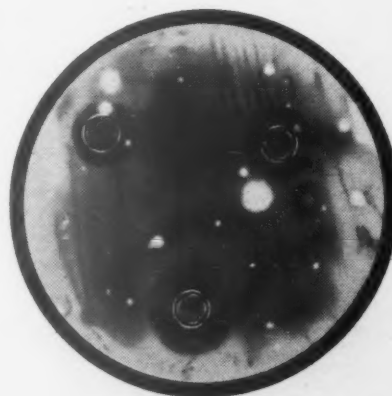
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With type as well as amount of fat in the human diet now assuming such importance, the new role of corn oil as a source of unsaturated fatty acids has prompted these questions:

1 What is the role of unsaturated fats in the daily diet?

answer: There is now ample clinical evidence that unsaturated fats tend to lower the serum cholesterol level of human subjects, whereas saturated fats have the opposite effect.

2 How much of the important unsaturated fatty acids does corn oil provide?

answer: MAZOLA Corn Oil yields an average of 85 per cent unsaturated fatty acids. 100 grams of MAZOLA will yield: 53 grams of linoleic acid and 28 grams of oleic acid; it also provides 1.5 grams of sitosterols, and only 12 grams of saturated fatty acids.

3 What is the best way to provide unsaturated fatty acids?

answer: By balancing the types of fat in the daily diet. Many doctors now agree that from one third to one half of the total fat intake should be in the form of a vegetable oil such as corn oil (MAZOLA).

4 How is corn oil most easily taken in the usual daily diet?

answer: There is no need to disturb the daily routine of meals or to have separate diets for individual members of the family. MAZOLA Corn Oil can be used instead of solid fats in preparing and cooking foods, it is also ideal for salad dressings.

5 How can I obtain further information on the value of corn oil as a source of unsaturated fatty acids?

answer: The subject is reviewed in the book "Vegetable Oils in Nutrition." Also available is a recipe book for distribution to your patients. It tells how to use corn oil in everyday meals. Both books will be sent free of charge to physicians, on request.



CORN PRODUCTS REFINING COMPANY
17 Battery Place, New York 4, N. Y.



Integral...

*in almost every diet
in health and disease*

For protein of excellent quality

For quickly available energy

For important B vitamins

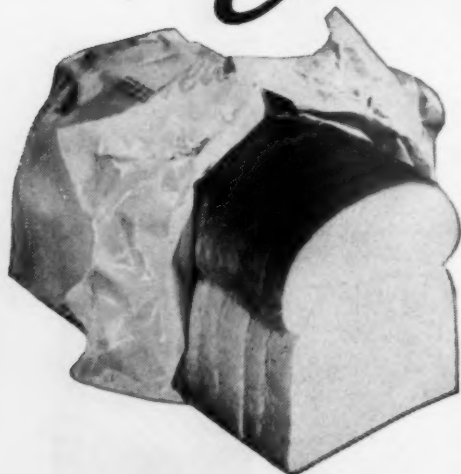
For essential minerals

For freedom from irritant residue

For low fat content

For taste and compatibility

Enriched Bread



is in Step with the Demands of
Advancing Nutritional Knowledge
Regardless of Dietary
Adjustment Needed

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive


•

Chicago 6, Illinois

**in common
mixed
infections**
...tetracycline
phosphate
alone

**in potentially
serious
infections**
...tetracycline
phosphate
plus
novobiocin

**for the
7 monilia-
susceptible
types**
...tetracycline
phosphate
plus
nystatin



**YOUR
CLINICAL
JUDGMENT
DICTATES
THE
CHOICE**

**in common
mixed
infections**
...tetracycline
phosphate
alone

**in potentially
serious
infections**
...tetracycline
phosphate
plus
novobiocin

**for the
7 monilia-
susceptible
types**
...tetracycline
phosphate
plus
nystatin

**PANMYCIN
Phosphate**

for children:

**PANMYCIN
Syrup**

PANALBA

for children:

**PANALBA
Granules**

COMYCIN

Upjohn

The Upjohn Company, Kalamazoo, Michigan

CIN*

te

CIN KM

TRADEMARK

**BROAD-SPECTRUM
TETRACYCLINE
IN ITS MOST
EFFICIENT FORM**

Produces more tetracycline in the blood with no more in the dose. No calcium to depress blood levels.¹ Basic broad-spectrum therapy in bronchitis, pharyngitis, otitis media, tonsillitis, and other common respiratory infections.

1. Welch, H.; Wright, W. W.; and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 4:620, 1957.

A*

A KM

**THE BREADTH OF
PANMYCIN PHOSPHATE PLUS
THE ANTIMICROCOCCAL
DEPTH OF ALBAMYCIN**

Offers maximum antimicrobial action at the earliest possible moment. The antibiotic preparation of first resort in pneumonia of unknown etiology, carbuncles, multiple furunculosis, cellulitis, and infections resistant to previous therapy.

Trademark of the Ciba Company, Inc., New York, N.Y.

N*

**PANMYCIN PHOSPHATE
PLUS THE ANTIMONILIAL
PROTECTION OF NYSTATIN**

The logical choice for patients requiring high doses of antibiotics or prolonged antibiotic therapy; for patients with previous monilial complications; for diabetics; patients on corticoids; the pregnant, debilitated, or elderly; and for infants, especially the premature.

THE CHOICE OF A SYSTEMIC ANTIBIOTIC IS A MATTER OF CLINICAL JUDGMENT

1. PANMYCIN PHOSPHATE IN COMMON MIXED INFECTIONS

USUAL DOSAGE: ADULTS: 250 mg. every 6 hours or 500 mg. every 12 hours. CHILDREN: Approximately 8 mg. per pound of body weight daily, in four equally divided doses every 6 hours, or two equally divided doses every 12 hours.

SUPPLIED: CAPSULES: 250 mg. in bottles of 16 and 100; 125 mg. in bottles of 25 and 100.

PANMYCIN KM SYRUP: Each teaspoonful (5 cc.) contains tetracycline equivalent to 125 mg. tetracycline hydrochloride, and potassium metaphosphate, 100 mg., mint flavor, in 2 fluidounce and pint bottles.

2. PANALBA IN POTENTIALLY SERIOUS INFECTIONS

USUAL DOSAGE: ADULTS: 1 or 2 capsules three or four times a day, depending on the type and severity of the infection. CHILDREN: Proportionately less.

SUPPLIED: Each powder-blue-and-brown capsule contains Panmycin (tetracycline) Phosphate complex equivalent to 250 mg. tetracycline hydrochloride, and Albamycin (as novobiocin sodium) 125 mg.; in bottles of 16 and 100.

Also available: **PANALBA KM GRANULES** (Pediatric). When reconstituted, each 5 cc. teaspoonful contains Panmycin equivalent to tetracycline hydrochloride, 125 mg. and Albamycin (as novobiocin calcium) 62.5 mg., and potassium metaphosphate 100 mg.; in pleasantly flavored vehicle. Dosage is based upon amount of tetracycline—6 to 8 mg. per pound of body weight per day in 2 to 4 equally divided doses.

3. COMYCIN FOR THE 7 MONILIA- SUSCEPTIBLE TYPES

USUAL DOSAGE: ADULTS: 1 or 2 capsules every 6 hours. CHILDREN: Proportionately less.

SUPPLIED: Each brown-and-pink capsule contains tetracycline phosphate complex, equivalent to 250 mg. tetracycline hydrochloride; nystatin 250,000 units. In bottles of 16 and 100.

Upjohn

The Upjohn Company, Kalamazoo, Michigan

effective, selective therapy

Cantil

for the colon

for functional and organic disorders

CANTIL relieves pain, cramps, bloating...curbs diarrhea...restores normal tone and motility. Selective action focused on the colon avoids widespread interference with normal autonomic function...minimizes urinary retention, mouth dryness, blurring of vision.

HOW CANTIL IS PRESCRIBED One or two tablets three times a day preferably with meals, and one or two tablets at bedtime for patients with ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

CANTIL—TWO FORMS CANTIL (plain)—25 mg. of CANTIL in each scored tablet—bottles of 100. CANTIL with Phenobarbital—25 mg. of CANTIL and 16 mg. of phenobarbital (warning: may be habit forming) in each scored tablet—bottles of 100.

CANTIL is the *only* brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

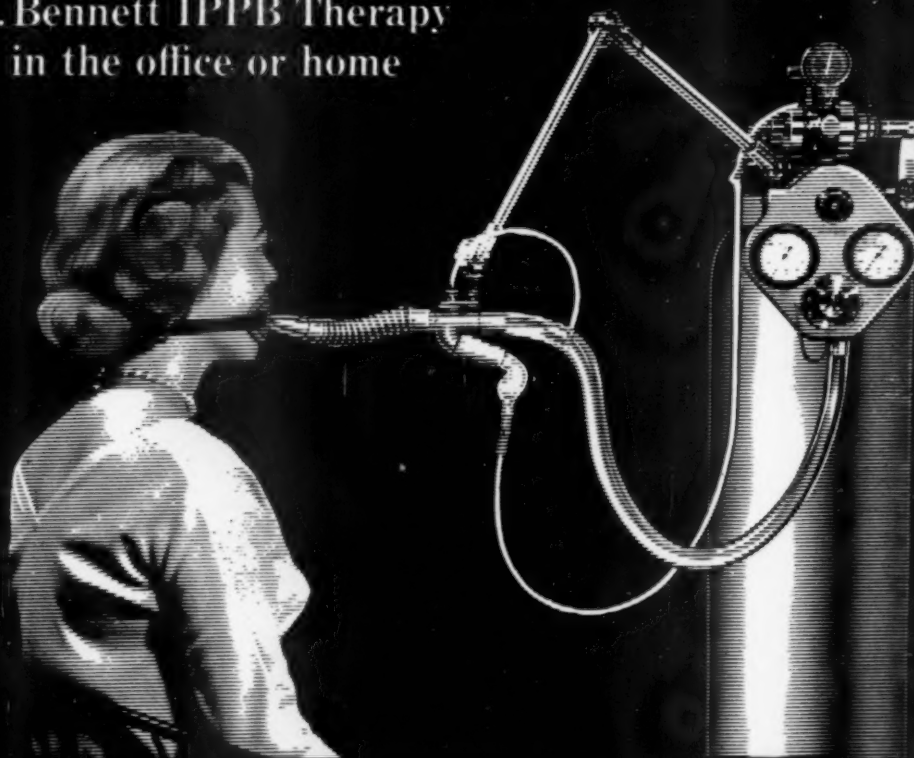
For more detailed information, request Brochure No. NDA 16, Lakeside Laboratories, Milwaukee 1, Wisconsin.

 **LAKESIDE**

14457



For your "breathless" patient...
 ...Bennett IPPB Therapy
 in the office or home



Authoritative recognition has repeatedly been accorded to the Bennett Pressure Breathing Therapy Unit for the most efficient treatment by intermittent positive pressure breathing (IPPB) of emphysema, asthma, bronchiectasis, and other conditions with acute or chronic dyspnea.

"Intermittent-positive-pressure breathing (IPPB), may be defined as a technique by which the lungs are actively inflated by means of a regulated, slightly positive pressure during inspiration, after which, during expiration, the lungs are passively deflated to atmospheric pressure, primarily by the elasticity of the lungs and the chest wall. The maximal peak pressure usually employed is that of 20 cm. of water, which is about one-fifth the maximal peak pressure that may be produced by a cough. The intermittent-positive-pressure breathing is produced by a type of respirator with a cycling valve operated by the gas pressure in the oxygen cylinder. A very slight inspiratory suction by the patient trips the cycling valve, and the positive pressure builds up during the inspiratory phase to the maximal peak pressure for which the regulator is set, after which the valve cycles and the pressure drops to atmospheric pressure during exhalation. The apparatus produces better depth of breathing, greater excursions of the diaphragm, and more uniform ventilation of the air sacs than that produced by the individual's own ambient breathing." Motley, H. L.: Evaluation of Function Impairment and New Developments in Therapy of Chronic Pulmonary Disease. A. M. A. Archives of Industrial Hygiene and Occupational Medicine, June, 1952, Vol. 5, pp 554-565.

Write for medical reprints and descriptive literature



BENNETT RESPIRATION PRODUCTS, INC.

2230 So. Barrington Avenue • Los Angeles 64, California

A subsidiary of Puritan Compressed Gas Corporation

WHEN ABORTION THREATENS...

CLINICALLY EFFECTIVE THERAPY BY MOUTH



NORLUTINTM

(norethindrone, Parke-Davis)

oral progestogen with unexcelled potency and unsurpassed efficacy

In obstetric complications amenable to progestational therapy, the clinical effects of injected progesterone can now be produced by small oral doses of NORLUTIN. For example, one investigator reports that 20 of 21 patients treated for threatened abortion appeared to benefit from administration of NORLUTIN.*

CASE SUMMARY* A 39-year-old married woman with a history of slight dysmenorrhea and staining intermittently superimposed on a regular 28-day cycle was placed on a regimen of stilbestrol. Staining recurred in spite of increasing dosage. Nearly two months after institution of this therapy a pregnancy of 16-weeks duration was discovered. Spotting continued during the following two weeks. Stilbestrol was then discontinued and treatment with NORLUTIN begun. Staining ceased 3 days after beginning treatment with NORLUTIN. The pregnancy continued uneventfully to full term when she gave birth to a healthy male infant weighing 6 pounds, 5 ounces.

INDICATIONS FOR NORLUTIN: Conditions involving deficiency of progestogen such as primary and secondary amenorrhea, menstrual irregularity, functional uterine bleeding, endocrine infertility, habitual abortion, threatened abortion, premenstrual tension, and dysmenorrhea.

PACKAGING: 5 mg. scored tablets (C. T. No. 882), bottles of 30.

*Abramson, D.: Personal communication.



PARKE, DAVIS & COMPANY — DETROIT 32, MICHIGAN

WORKING



with **STERANE[®]**

brand of prednisolone

ARTHRITIC patients on STERANE can achieve a manual dexterity, dramatic in degree — frequently after salicylates and/or previous corticoids have proved unsatisfactory — with minimal incidence of electrolyte imbalance.

White, scored 5 mg. tablets (bottles of 20 and 100);
pink, scored 1 mg. tablets (bottles of 100).



PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.



"Doctors can't help shingles?"

Physicians who have used PROTAMIDE extensively deplore such statements as unfortunate when they appear in the lay press. They

have repeatedly observed in their practice quick relief of pain,

even in severe cases, shortened duration of lesions, and greatly lowered incidence of postherpetic neuralgia when

PROTAMIDE was started promptly. A folio of reprints is available. These papers report on zoster in the elderly—

the severely painful cases—patients with extensive lesions. PROTAMIDE users know "shingles" *can* be helped.



PROTAMIDE®

Sherman Laboratories

Detroit 11, Michigan

Available: Boxes of 10 ampuls—prescription pharmacies.

Now from **American
Sterilizer—**

***MODEL 613-R PORTABLE HIGH-SPEED AUTOCLAVE**

**New HIGH in performance
New LOW in cost**



The newest product of the world's
largest manufacturer of Pressure
Steam Sterilizers

See your authorized
American Sterilizer Dealer or write
for Bulletin DC-410.

THESE FEATURES:

All Stainless Steel

For durability and easy cleaning

Positive Sterilization

Pressure steam at 250° F. to 270° F.

Greater Capacity

Holds three large trays (6" x 13")

Fast

Reaches 270° F. in approximately
seven minutes

Automatic

Times any selected sterilizing cycle

Cool and Dry

Dries instruments or supplies by ex-
hausting steam and residual water
back into water reservoir . . . NOT
into room

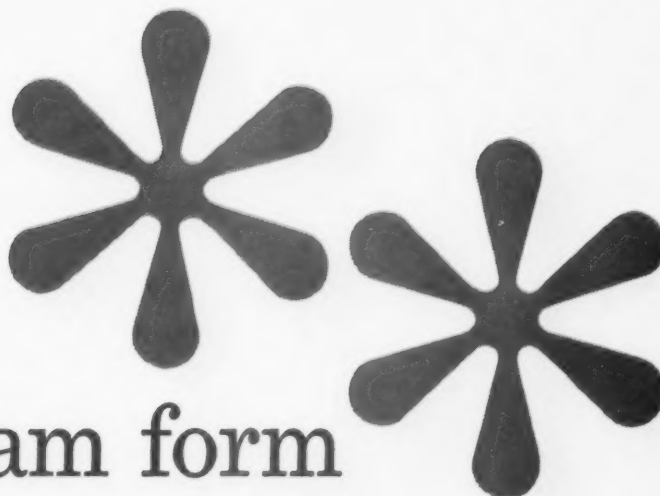
**Safety-Lock Door, Adjust-
able Thermostat and Accurate
Temperature Gauge**

Automatically "burn-out" proof

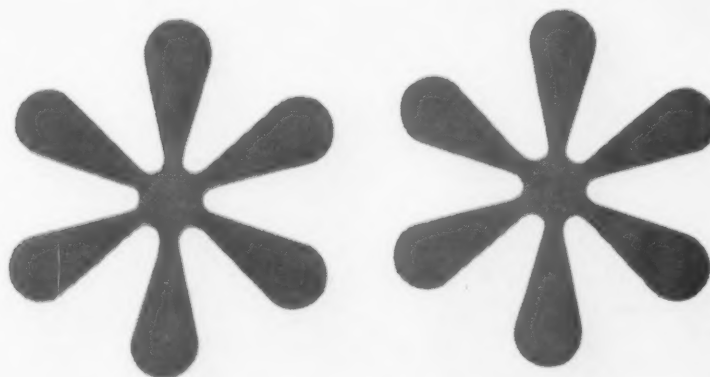


STERILIZER

ERIE • PENNSYLVANIA



now in cream form



STEROSAN[®] Hydrocortisone

(chlorquinaldol GEIGY with hydrocortisone)

cream

comprehensive control of skin disorders

infectious dermatoses • contact dermatitis • atopic dermatitis • nonspecific pruritus

- * combats infection
- * reduces inflammation
- * controls itching
- * promotes healing

STEROSAN[®]-Hydrocortisone (3% chlorquinaldol GEIGY with 1% hydrocortisone) Cream and Ointment. Tubes of 5 Gm. Prescription only.

and when a nonsteroid preparation is preferred STEROSAN[®] (chlorquinaldol GEIGY) 3% Cream and Ointment. Tubes of 30 Gm. and jars of 1 lb. Prescription only.

GEIGY

Ardsley, New York



freedom from asthma

... thanks to Tedral prescribed by his physician.

*No single drug can equal Tedral to protect
the asthmatic patient against symptoms 'round the clock.*

Dosage: 1 or 2 tablets q.i.d. Available: boxes of 24, 120 and 1,000.

Tedral[®]

a product of Warner-Chilcott

New...from Pfizer Research

84

compounds tested

1

compound unexcelled

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

Progress has been made in antibiotic therapy through the use of absorption-enhancing agents, resulting in higher, more effective antibiotic blood levels.

For the past two years, in a continuing search for more effective agents for enhancing oral antibiotic blood levels, our Research Laboratories screened eighty-four adjuvants, including sorbitol, citric acid, sodium hexametaphosphate, and other organic acids and chelating agents as well as phosphate complex and other analogs. After months of intensive comparative testing, glucosamine proved to be the absorption-enhancing agent of choice. Here's why:

1 Crossover tests show that average blood levels achieved with glucosamine were markedly higher than those of other enhancing agents screened. In some cases this effect was more than double.

2 Of great importance to the practicing physician is the consistency of the blood level enhancement achieved with glucosamine. Extensive tests show that the enhancing effect with glucosamine occurs in a greater percentage of cases than with any other agent screened.

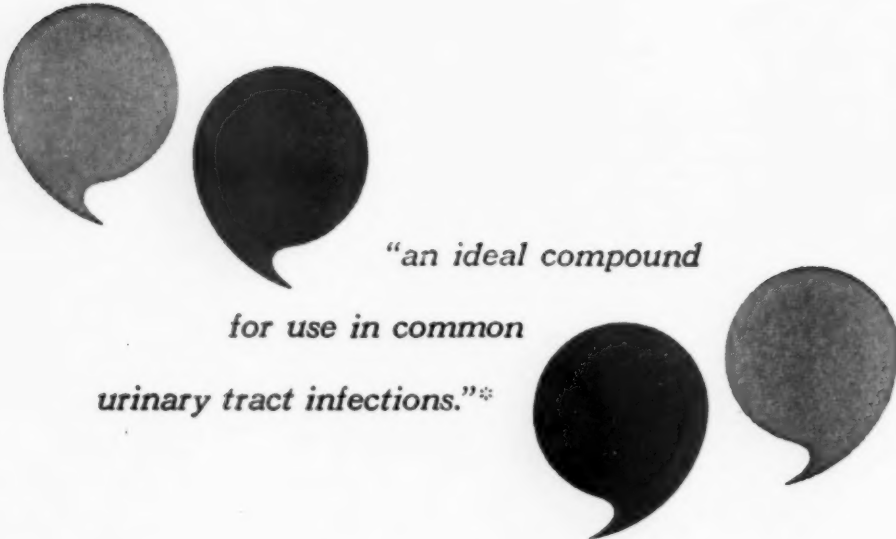
3 Glucosamine is a nontoxic physiologic metabolite occurring naturally and widely in human secretions, tissues and organs. It is nonirritating to the stomach, does not increase gastric secretion, is sodium free and releases only four calories of energy per gram. Also, there is evidence that glucosamine may favorably influence the bacterial flora of the intestinal tract.

For these reasons glucosamine provides you with an important new adjuvant for better enhancement of antibiotic blood levels. Tetracycline, potentiated physiologically with glucosamine, is now available to you as COSA-TETRACYN.

Capsules 250 mg. and 125 mg.

The most widely used
broad-spectrum antibiotic
now potentiated with
glucosamine, the
enhancing agent of choice

*Trademark



*"an ideal compound
for use in common
urinary tract infections."**

Azo Gantrisin provided "prompt and effective clearing of organisms and pyuria"* plus "dramatic relief of bladder and urethral symptoms"* in 221 (97%) of 228 patients with urinary tract infections.

Azo Gantrisin is particularly useful in the treatment of cystitis, urethritis and prostatitis. It is equally valuable following urologic surgery, cystoscopy and catheterization because it provides effective antibacterial action plus prompt pain relief.

AZO GANTRISIN®—500 mg Gantrisin (brand of sulfisoxazole) plus 50 mg phenylazo-diamino-pyridine HCl

*F. K. Garvey and J. M. Lancaster, North Carolina M. J., 18:78, 1957.

AZO GANTRISIN 'Roche'

ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC • NUTLEY • N. J.

ORIGINAL RESEARCH IN MEDICINE AND CHEMISTRY

1

UNEXCELLED

HEIGHT

of tetracycline
blood levels
achieved

new

with

COSA-TETRACYN

GLUCOSAMINE-POTENTIATED TETRACYCLINE

The most widely
used broad-spectrum
antibiotic now
potentiated
with glucosamine,
the enhancing
agent of choice

Capsules 250 mg.
125 mg.

*Trademark





*when every
meal's a 'quick
energy' snack*

...or when a diet goes
wrong for *any* reason,
what's probably needed
first...and *most*...
is the essential B-com-
plex. That's a good
time to remember.

*Coming your way in
color next month,
Doctor. Watch for them
in your mail in March.

a good B-complex

sur-Bex[®] with C

(Abbott's B-Complex Tablets with C)

Just one Sur-Bex with C tablet a day represents:

Thiamine Mononitrate.....	6 mg.
Riboflavin.....	6 mg.
Nicotinamide.....	30 mg.
Pyridoxine Hydrochloride.....	1 mg.
Vitamin B ₁₂	2 mcg.
Calcium Pantothenate.....	10 mg.
Ascorbic Acid.....	150 mg.
Desiccated Liver, N. F.....	300 mg.
Brewer's Yeast, Dried.....	150 mg.

As a dietary supplement: 1 or 2 tablets daily
In convalescence: 2 or more tablets daily

Abbott

802079

2

UNEXCELLED

CONSISTENCY

of higher
tetracycline
blood levels

new

achieved with

COSA-TETRACYN*

GLUCOSAMINE-POTENTIATED TETRACYCLINE

Pfizer

The most widely
used broad-spectrum
antibiotic now
potentiated
with glucosamine,
the enhancing
agent of choice

Capsules 250 mg.,
125 mg.

*Trademark

Meat...

and Protein Nutrition in Vascular Disease

Whether the eventual solution of the problem of atherogenesis will come out of the field of dietetics, biophysics, or pharmacology, one fact remains undeniable:

Adequate protein nutrition is considered of importance for the age group most commonly affected by disease of the vascular system, so that the demands of good nutritional health might be met.

Meat is outstanding among protein foods. It supplies all the essential amino acids, and closely approaches the quantitative proportions needed for biosynthesis of human tissue.

In addition, it is an excellent source of B vitamins, including B₆ and B₁₂, as well as iron, phosphorus, potassium, and magnesium.

When curtailment of fat intake is deemed indicated, meat need not always be denied the patient. Visible fat obviously should not be eaten. But the contained percentage of invisible (interstitial) fat is well within the limits of reasonable fat allowance.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

3

UNEXCELLED

PHYSIOLOGIC ADVANTAGES

of glucosamine,
a normal human

new

metabolite, in

COSA-TETRACYN

GLUCOSAMINE-POTENTIATED TETRACYCLINE

Pfizer

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

The most widely
used broad-spectrum
antibiotic now
potentiated
with glucosamine,
the enhancing
agent of choice

Capsules 250 mg.,
125 mg.

*Trademark

IN

PATIENT

AFTER

PATIENT

ARMOUR **thyroid**

unsurpassed in quality and
for consistent therapeutic
results.

Indicated in
myxedema and other frank thy-
roid deficiencies
when hypothyroidism is involved

- chronic recurrent colds
- postpartum fatigue
- functional menstrual disorders
- sterility
- habitual abortion
- certain anemias
- obesity
- hypometabolism

No other thyroid product has been used so widely and so often by leading physicians everywhere. On your prescriptions *specify* ARMOUR Thyroid.



THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS



FOR PROMPT UTILIZATION

AND BETTER STORAGE

HOMAGENETS®

The only homogenized vitamins in solid form

Homagenets are unusually palatable—and good taste is especially important to your patients. Of more interest to the physician is the homogenization process. This presents both oil and water soluble vitamins in microscopic particles. Thus the vitamins in Homagenets are better absorbed and utilized—and stored longer.¹ These are definite advantages to your patient.

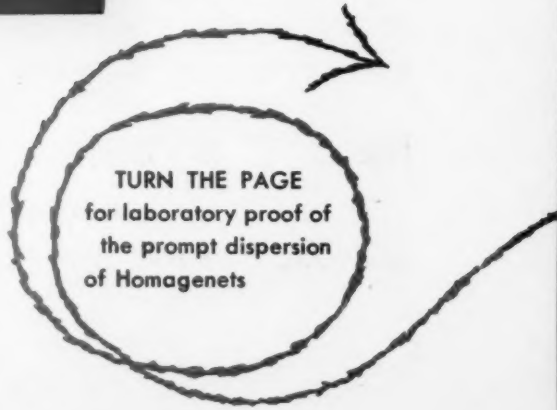
1. Lewis, J.M., et al.: *J. Pediat.* 31:496.

**THE
ADVANTAGES
OF
HOMAGENETS**

Pleasant, candy-like flavor
Better absorbed, better utilized
Excess vitamin dosage unnecessary
Longer storage in the body
No regurgitation, no "fishy burp"
May be chewed, swallowed or
dissolved in the mouth.

Homagenets are available in five formulas: Prenatal, Pediatric, Therapeutic, Geriatric and Aoral (brand of vitamin A).

THE S. E. MASSENGILL COMPANY
Bristol, Tennessee



TURN THE PAGE
for laboratory proof of
the prompt dispersion
of Homagenets



**VISUAL
PROOF OF
THE RAPID
DISPERSION
OF
HOMAGENETS**

These photographs show the dispersion time of a Homagenet and a soft gelatin capsule in artificial gastric juice at 37°C.

Homagenets are available in five formulas: Prenatal, Pediatric, Therapeutic, Geriatric and Aroal (brand of vitamin A).

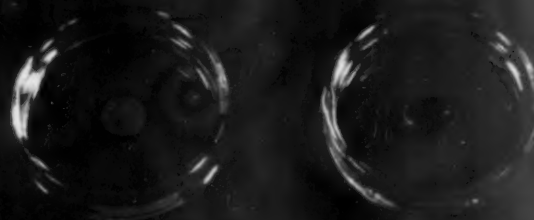
Currently, mailings will be forwarded only at your request.

Write for samples and literature.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

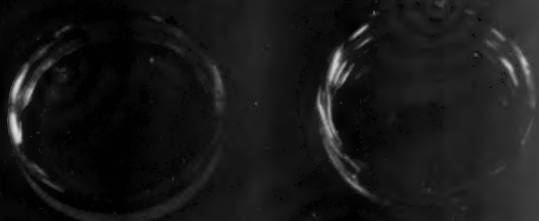
NEW YORK • KANSAS CITY • SAN FRANCISCO



1. Immediately after placement in Petri dishes.



2. Six minutes later.



3. Twelve minutes later.



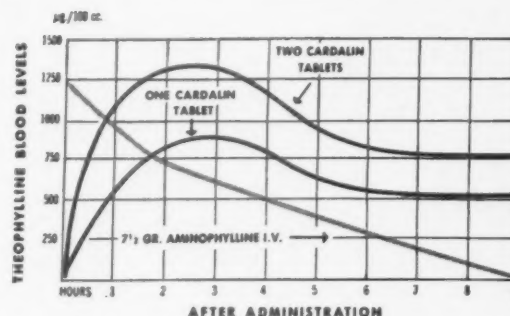
4. Two hours and 12 minutes later.

Orally... higher and more sustained aminophylline blood levels than those produced intravenously

Cardalin utilizes two synergistic protective factors to permit administration of high oral doses of aminophylline without the usual side effects of nausea, gastric irritation and vomiting.

CARDALIN

... proven effective clinically whenever high blood concentrations of aminophylline are desired ... as in congestive heart failure, cardiac edema, paroxysmal dyspnea, angina pectoris, myocardial infarction, heart block and bronchial asthma.



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11:301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100:309, 1950.)

Each Cardalin tablet supplies: Aminophylline, 5.0 gr.; Aluminum hydroxide, 2.5 gr.; Ethyl aminobenzoate, 0.5 gr.

Also available, Cardalin-Phen.

Neisler

Irwin, Neisler & Co. • Decatur, Illinois

when anxiety and tension "erupts" in the G. I. tract... IN GASTRIC ULCER



PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer ... helps control the "emotional overlay" of gastric ulcer — without fear of barbiturate loginess, hangover or habituation ... *with* PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime.

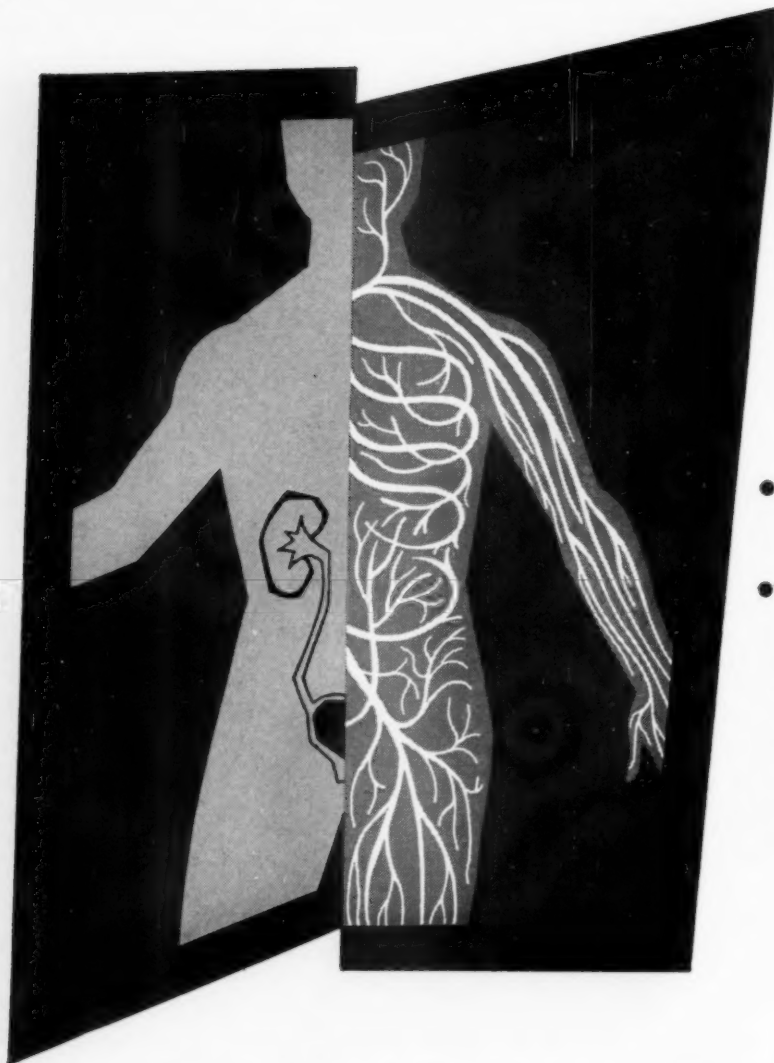
Supplied: Bottles of 100, 1,000.

Lederle

*Trademark

®Registered Trademark for Tridihexethyl Iodide Lederle

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK



- Angiography
- Intravenous and retrograde urography

*Versatile radiological agents with
an unexcelled degree of safety*

RENOGRAFIN

Squibb Contrast Media

- well tolerated systemically and locally
- consistently good visualization
- convenient concentrations, in easily administered form

RENOGRAFIN 76%

for intravenous urography and angiography. Ampuls of 20 cc., with 1 cc. ampul for sensitivity testing. Each cc. contains 760 mg. of sodium and methylglucamine diatrizoate.

RENOGRAFIN 60%

for intravenous urography and angiography. Ampuls of 25 cc., with 1 cc. ampul for sensitivity testing. Each cc. contains 600 mg. of sodium and methylglucamine diatrizoate.

RENOGRAFIN 30%

for retrograde pyelography. Rubber-capped vials of 50 cc. Each cc. contains 299 mg. of sodium and methylglucamine diatrizoate.

*RENOGRAFIN® IS A SQUIBB TRADEMARK

SQUIBB



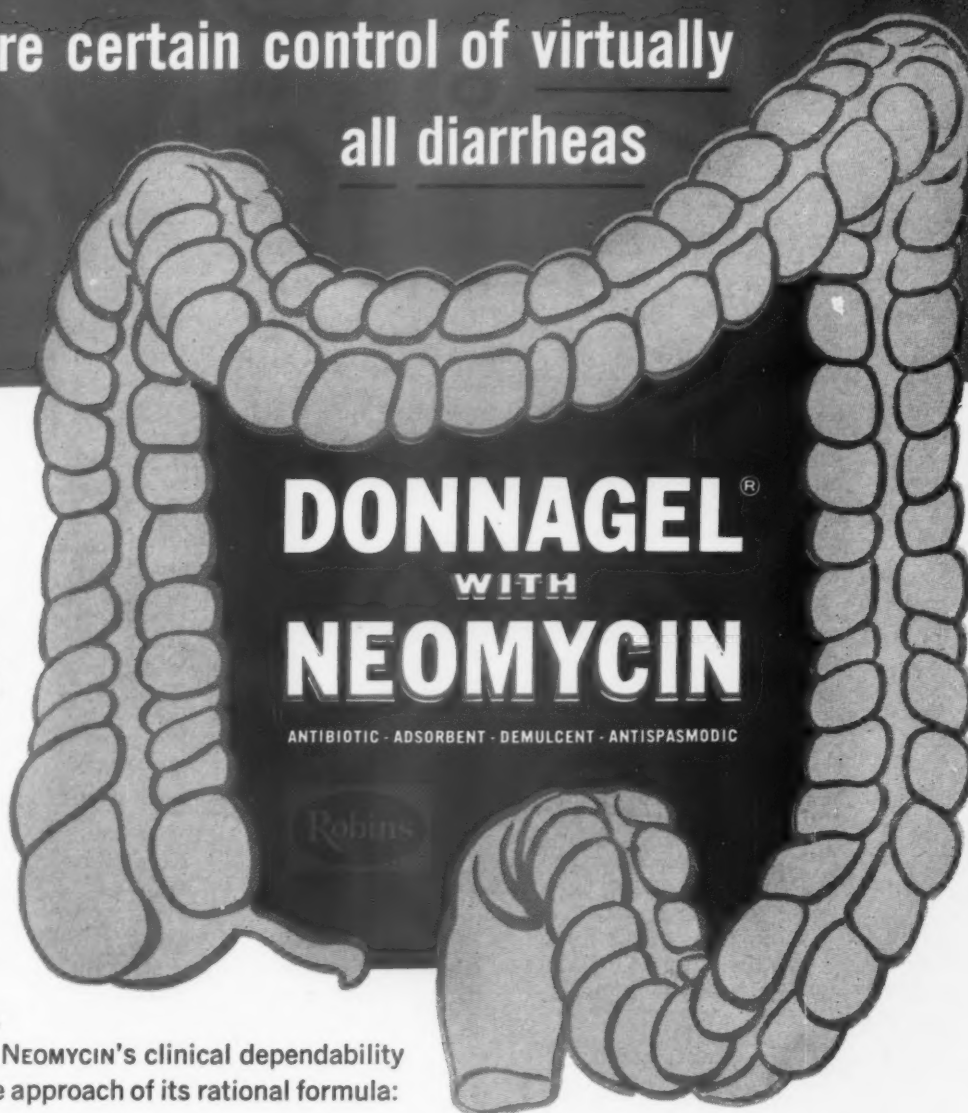
Squibb Quality — the Priceless Ingredient

*- the
preparation
you've
asked
for*

ANNOUNCING: a NEW antidiarrheal for more certain control of virtually all diarrheas

Addition of neomycin to the effective DONNAGEL formula assures even more certain control of most of the common forms of diarrhea. Neomycin is an ideal antibiotic for enteric use: it is effectively bacteriostatic against neomycin-susceptible pathogens; and it is relatively non-absorbable.

The secret of DONNAGEL WITH NEOMYCIN's clinical dependability lies in the comprehensive approach of its rational formula:



DONNAGEL[®] WITH NEOMYCIN

ANTIBIOTIC - ADSORBENT - DEMULCENT - ANTISPASMODIC

Robins

Robins

Informational
literature
available
upon request.

COMPONENT in each 30 cc. (1 fl. oz.)	ACTION	BENEFIT
Neomycin base, 210.0 mg. (as neomycin sulfate, 300 mg.)	antibiotic	Affords effective intestinal bacteriostasis.
Kaolin (6.0 Gm.)	adsorbent, demulcent	Binds toxic and irritating substances. Provides protective coating for irritated intestinal mucosa.
Pectin (142.8 mg.)	protective, demulcent	Supplements action of kaolin as an intestinal detoxifying and demulcent agent.
Dihydroxyaluminum aminoacetate (0.25 Gm.)	antacid, demulcent	Enhances demulcent and detoxifying action of the kaolin-pectin suspension.
Natural belladonna alkaloids: hyoscyamine sulfate (0.1037 mg.) atropine sulfate (0.0194 mg.) hyoscine hydrobromide (0.0065 mg.)	anti- spasmodic	Relieves intestinal hypermotility and hypertonicity.
Phenobarbital (1/4 gr.)	sedative	Diminishes nervousness, stress and apprehension.

INDICATIONS: DONNAGEL WITH NEOMYCIN is specifically indicated in diarrheas or dysentery caused by neomycin-susceptible organisms; in diarrheas not yet proven to be of bacterial origin, prior to definitive diagnosis. Also useful in enteritis, even though diarrhea may not be present.
SUPPLIED: Bottles of 6 fl. oz. At all prescription pharmacies.

DOSAGE: Adults: 1 to 2 tablespoonfuls (15 to 30 cc.) every 4 hours. Children over 1 year: 1 to 2 teaspoonfuls every 4 hours. Children under 1 year: 1/2 to 1 teaspoonful every 4 hours.
ALSO AVAILABLE: DONNAGEL, the original formula, for use when an antibiotic is not indicated.

hypertension, tachycardia, agitation
controlled through sympathetic regulation*



*When stress disturbs sympathetic balance...by eliciting increased activity of the sympathetic nervous system...hypertension, tachycardia, agitation and many other symptoms you see in daily practice may result. Through its unique ability to regulate sympathetic function, Serpasil controls these symptoms. In hypertension, sympathetic regulation by Serpasil reduces vasoconstriction, brings blood pressure down slowly and safely; in tachycardia, cardio-accelerator impulses are inhibited, the heart rate is slowed, and cardiac efficiency is enhanced; in emotional agitation and tension, Serpasil exerts a general calming effect by suppressing sympathetic activity in autonomic centers. It is also useful in treating premenstrual tension, menopausal syndrome, and acute and chronic alcoholism. Serpasil® (reserpine CIBA) is indeed one of the most versatile as well as one of the safest and least toxic agents in everyday practice.

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Presenting an advance in the treatment of
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 VAGINAL SUPPOSITORIES AND POWDER

85% CLINICAL CURES*

In 219 patients with either trichomonal vaginitis, monilial vaginitis or both, clinical cures were secured in 187.

71% CULTURAL CURES*

157 patients showed negative culture tests at 3 months follow-up examinations. Patients reported rapid relief of burning and itching, often within 24 hours.



STEP 1 Office administration of TRICOFURON VAGINAL POWDER **IMPROVED** at least once weekly.



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*Combined results of 12 independent clinical investigators. Data available on request.

SUPPOSITORIES:

0.375% Micofur, 0.25% Furoxone.

POWDER:

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"Mepro tabs" are new, *coated*, white, unmarked 400 mg. tablets of meprobamate. ■ "Mepro tabs" are pleasant tasting, and easy to swallow. ■ In this new form, the nature of medication is not identifiable by the patient. ■ "Mepro tabs" are indicated for the relief of anxiety, tension and muscle spasm in everyday practice. ■ *Usual dosage*: One or two tablets t.i.d.

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TO THE PHYSICAL AND MENTAL WELL-BEING
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IS THE SECONDARY ROLE OF THE OVARY..."***

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When the physician prefers estrogen-androgen therapy, "Premarin" with Methyltestosterone can be employed to good advantage as combined therapy.

*Masters, W.H.: Am. J. Obst. & Gynec., 74:733 (Oct.) 1957.



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distress can be alleviated with certainty
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natural "Premarin" contains *all* of the naturally occurring components of the equine estrogen complex.

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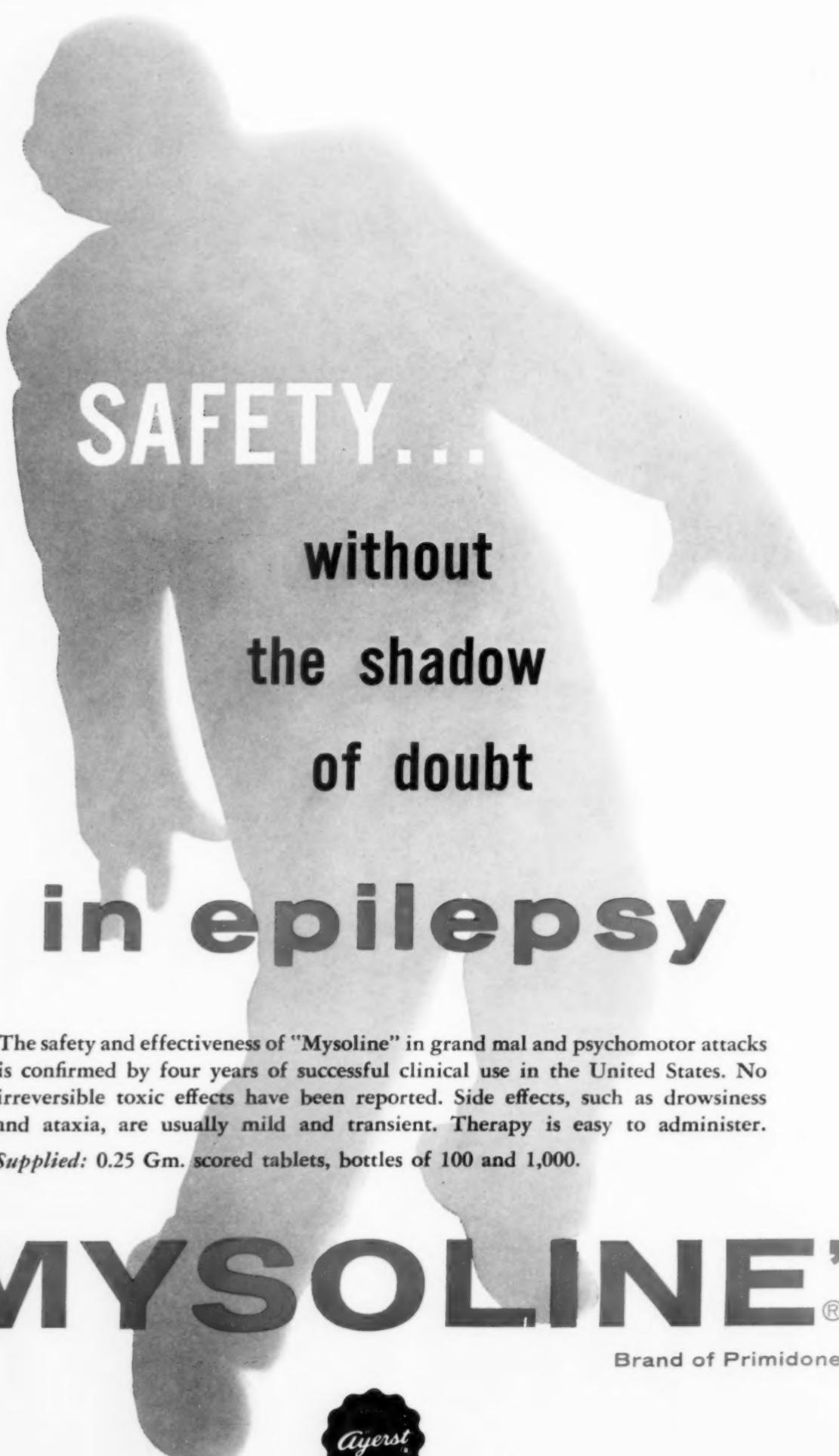
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without
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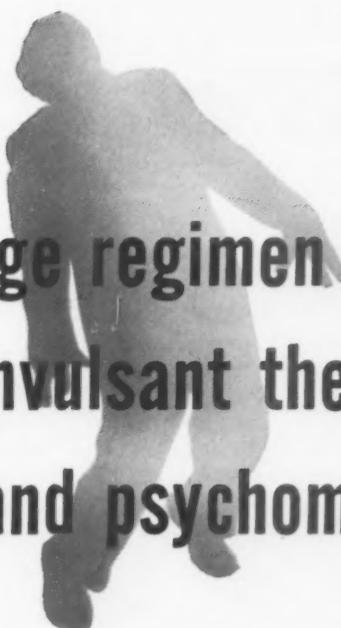
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"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

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**simple dosage regimen facilitates
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in grand mal and psychomotor attacks**

"MYSOLINE" is easy to administer

Adults and children (over 8 years):

1 tablet (0.25 Gm.) daily (preferably at bedtime) for 1 week.
Increase by 1 tablet weekly until control.

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Order of dosage same as for adults, but start with $\frac{1}{2}$ tablet (0.125 Gm.) daily and increase by $\frac{1}{2}$ tablet weekly, until control.

(Dosages exceeding 2 Gm. daily presently not recommended.)

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Supplied: "Mysoline,"® Brand of Primidone, 0.25 Gm. scored tablets, bottles of 100 and 1,000.



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A versatile, well-balanced formula capable of modifying the course of common upper respiratory infections . . . particularly valuable during respiratory epidemics; when bacterial complications are likely; when patient's history is positive for recurrent otitis, pulmonary, nephritic, or rheumatic involvement.

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Available on prescription only.

TABLETS (sugar coated) Each Tablet contains:

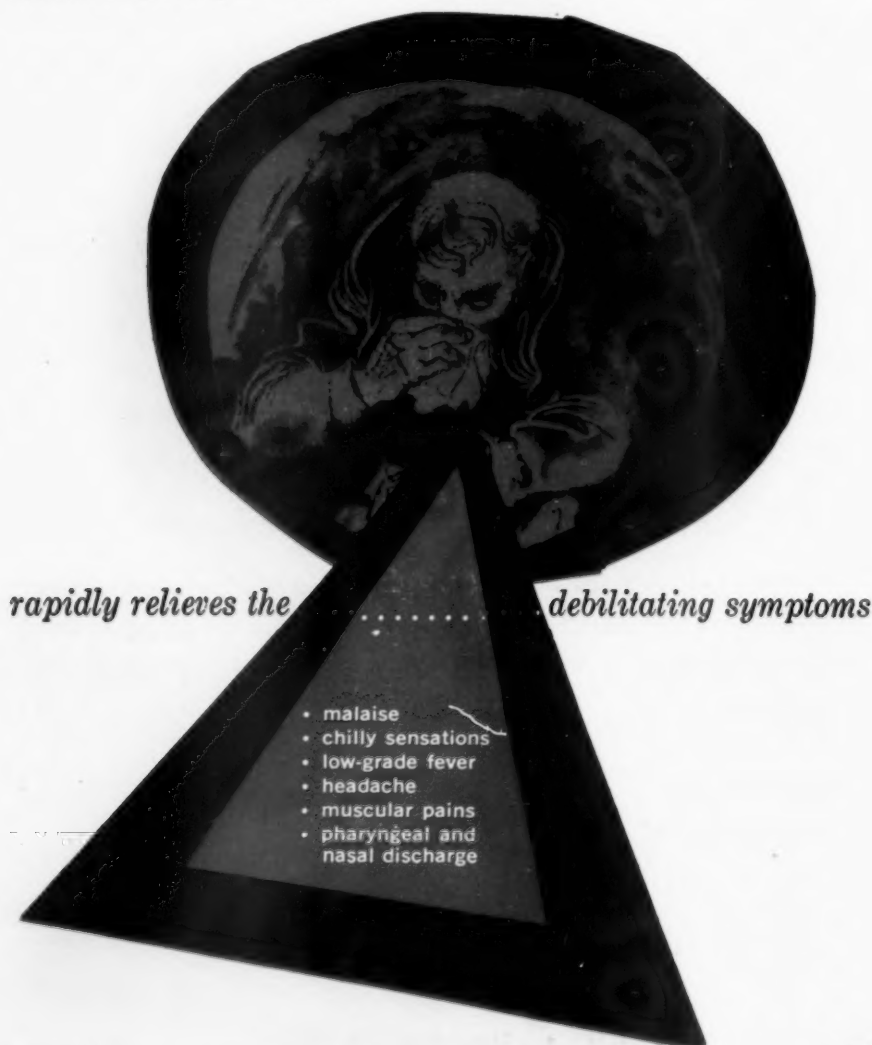
ACHROMYCIN® Tetracycline	125 mg.
Phenacetin	120 mg.
Caffeine	30 mg.
Salicylamide	150 mg.
Chlorothen Citrate	25 mg.

Bottles of 24 and 100.

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Salicylamide	150 mg.
Ascorbic Acid (C)	25 mg.
Pyrimamine Maleate	15 mg.
Methylparaben	4 mg.
Propylparaben	1 mg.

Bottle of 4 oz.



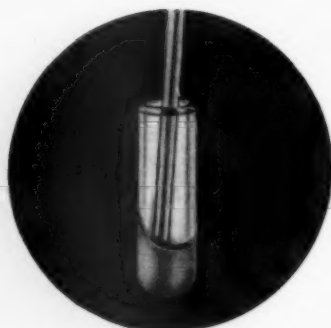
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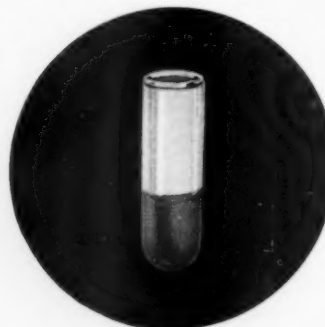
2. Crush tablet.



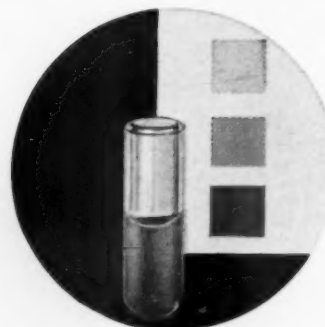
4. Add 1 drop
of color developer: mix.



1. Add 4 drops serum or plasma
to one PHOSPHATAB tablet
in special tube.



3. Let stand at room
temperature 12-30 minutes.
(time from chart)



5. Compare color.

**For the First Time: STAT ASSURANCE[®]
In These Common Diagnostic Problems:**

Uncertain bile duct involvement

Questionable retained stones in the bile duct

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For rapid economical semi-quantitative alkaline phosphatase levels

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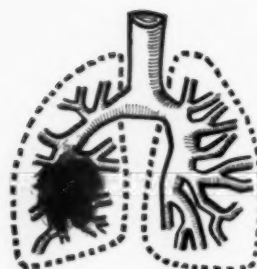
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*For wide-spectrum
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GANTRICILLIN

*provides Gantrisin plus penicillin
in a single tablet.....*



*for control of both gram-positive
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THE TRAL PATIENT

unbothered
by the
ulcer
or the
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marked selectivity in anticholinergic therapy

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IN LOW-BACK ACHE

**STOP
THE
MUSCLE
SPASM**

Disipal[®]*

Brand of Orphenadrine HCl

Relieves Spasm, Pain, and Depression too

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Highly selective action...energizing against weakness, fatigue, adynamia and akinesia...potent against sialorrhea, diaphoresis, oculogyria and blepharospasm...lessens rigidity and tremor...alleviates depression...safe...even in glaucoma.

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Patients with muscle spasm of the usual types demand relief first. Disipal fills this need. In sprains, strains, fibrositis, noninflammatory arthritic states and other musculoskeletal disorders, Disipal not only relieves the spasm, but alleviates the depression which so often accompanies pain of any type.

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Gantrisin



Gantrisin is useful — particularly for children — in influenza sequelae, pneumonia, tonsillitis, bronchitis and other nonspecific respiratory infections.

Gantrisin offers the advantage of an effective antibacterial with high solubility and little danger of renal complication.

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when anxiety and tension "erupts" in the G. I. tract...
IN DUODENAL ULCER



PATHIBAMATE*

Meprobamate with PATHILON® Lederle

Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of duodenal ulcer — without fear of barbiturate loginess, hangover or habituation . . . with PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime.

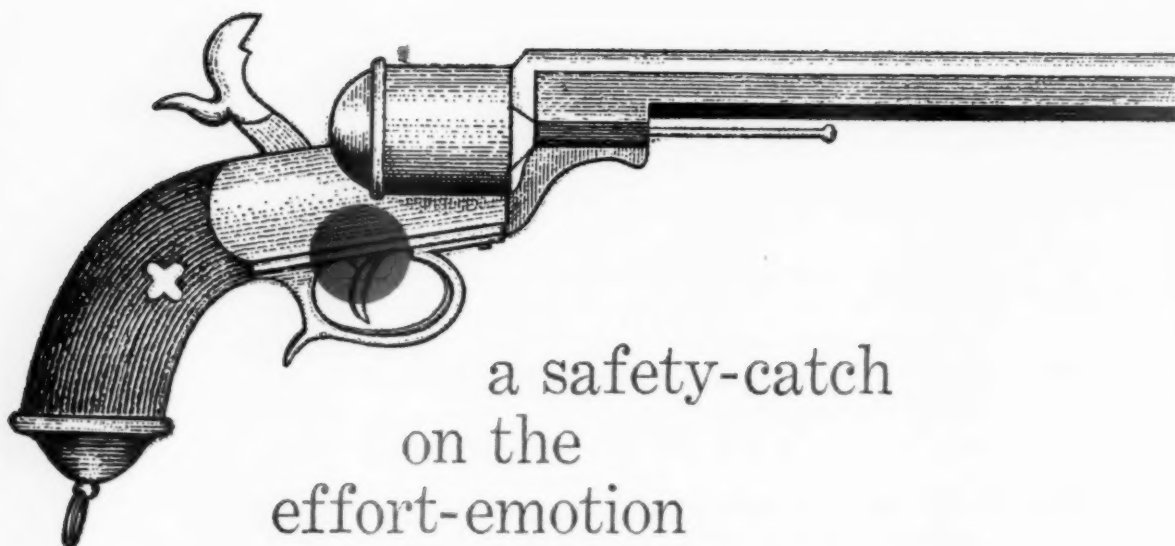
Supplied: Bottles of 100, 1,000.



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a safety-catch
on the
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"trigger"

new

Pentraline*

vasodilator • calmative

(formerly Pentrasine)

for comprehensive angina prophylaxis

PENTRALINE inhibits precipitating stimuli...helps reduce the severity and frequency of anginal attacks through the complementary action of its three components. Rauwolfia preparations and pentaerythritol tetranitrate, for example, when given together produce greater benefits than either drug used alone.¹ The reserpine alkaloid of rauwolfia also enhances the gentle sedation induced by Butisol Sodium® with mild, safe tranquilization. Thus PENTRALINE represents a comprehensive and rational approach to angina management. Plan to try PENTRALINE soon.

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Pentaerythritol Tetranitrate—10 mg.—best of the long-acting coronary vasodilators²

Butisol Sodium® Butabarbital Sodium—10 mg.—intermediate sedative ideally suited to long-term therapy³

Reserpine—0.05 mg.—effective adjunct in the management of angina pectoris^{1,4}

Suggested Dosage: One tablet four times a day before meals and at bedtime.

Note: PENTRALINE is not intended for treatment of acute attacks of angina pectoris, but rather for routine daily use as a preventive measure.

References: (1) Deitz, G. W.: *Am. Pract. & Digest. Treat.* 6:1872, 1955. (2) Russek, H. I.; Zohman, B. L.; Drumm, A. E.; Weingarten, W. and Dorset, V. J.: *Circulation* 12:169, 1955. (3) Dripps, R. D.: *J.A.M.A.* 139:148, 1949. (4) Lewis, B. I.; Lubin, R. C.; January, L. E., and Wild, J. B.: *Circulation* 14:227, 1956.

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NEW...

*A more potent,
more effective,
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With a powerful new adsorbent—having five times the adsorbent action of kaolin

With two synergistic antibiotics—having a more effective antidiarrheal spectrum (with systemic absorption so minimal as to preclude toxicity)

With increased potency—for greater therapeutic effectiveness, smaller dose

With refreshing taste—for acceptability in all age groups



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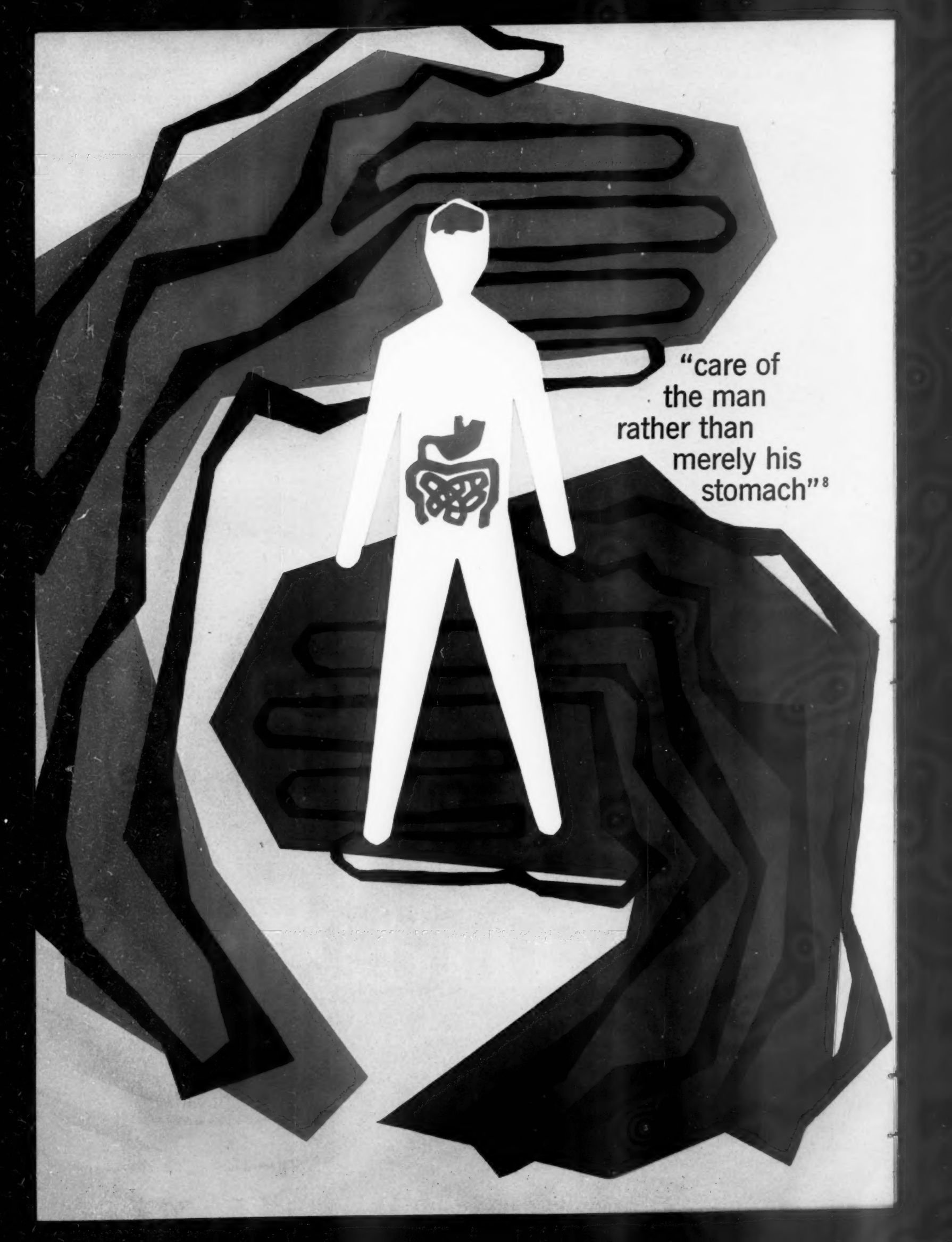
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Polymagma contains Polymyxin B Sulfate, Polymyxin E Sulfate, and Pectin with Kaopectate® (Activated Attapulgite, Wyeth Laboratories).




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Supplied: Bottles of 8 fl. oz.



"care of
the man
rather than
merely his
stomach"⁸

"Milpath"

Miltown®  anticholinergic

two-level control of gastrointestinal dysfunction

at the central level

The tranquilizer Miltown® reduces anxiety and tension.^{1,3,6,7}

Unlike the barbiturates, it does not impair mental or physical efficiency.^{5,7}

at the peripheral level

The anticholinergic tridihexethyl iodide reduces hypermotility and hypersecretion.

Unlike the belladonna alkaloids, it rarely produces dry mouth or blurred vision.^{2,4}

indications: peptic ulcer, spastic and irritable colon, esophageal spasm, G. I. symptoms of anxiety states.

each "Milpath" tablet contains:

Miltown® (meprobamate WALLACE) 400 mg.
(2-methyl-2-n-propyl-1,3-propanediol dicarbamate)
Tridihexethyl iodide 25 mg.
(3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethiodide)

dosage: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

available: bottles of 50 scored tablets.

references:

1. Altschul, A. and Billow, B.: The clinical use of meprobamate (Miltown®). *New York J. Med.* 57:2361, July 15, 1957. 2. Atwater, J. S.: The use of anticholinergic agents in peptic ulcer therapy. *J. M. A. Georgia* 45:421, Oct. 1956. 3. Borrus, J. C.: Study of effect of Miltown (2-methyl-2-n-propyl-1,3-propanediol dicarbamate) on psychiatric states. *J. A. M. A.* 157:1596, April 30, 1955. 4. Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer. *Am. J. Digest. Dis.* 1:301, July 1956. 5. Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Experimental studies of behavioral effects of meprobamate on normal subjects. *Ann. New York Acad. Sc.* 67:701, May 9, 1957. 6. Phillips, R. E.: Use of meprobamate (Miltown®) for the treatment of emotional disorders. *Am. Pract. & Digest Treat.* 7:1573, Oct. 1956. 7. Selling, L. S.: A clinical study of Miltown®, a new tranquilizing agent. *J. Clin. & Exper. Psychopath.* 17:7, March 1956. 8. Wolf, S. and Wolff, H. G.: *Human Gastric Function*, Oxford University Press, New York, 1947.



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YOU TREAT
INFECTIONS
IN PATIENTS
SUCH
AS THESE

- debilitated
- elderly
- diabetics
- infants, especially prematures
- those on corticoids
- those who developed moniliasis on previous broad-spectrum therapy
- those on prolonged and/or high antibiotic dosage
- women—especially if pregnant or diabetic

the best broad-spectrum antibiotic to use is

MYSTECLIN-V

Squibb Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)

Sumycin plus Mycostatin

for practical purposes, Mysteclin-V is sodium-free

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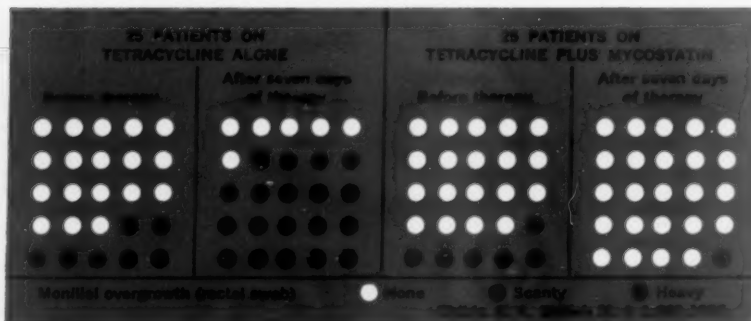
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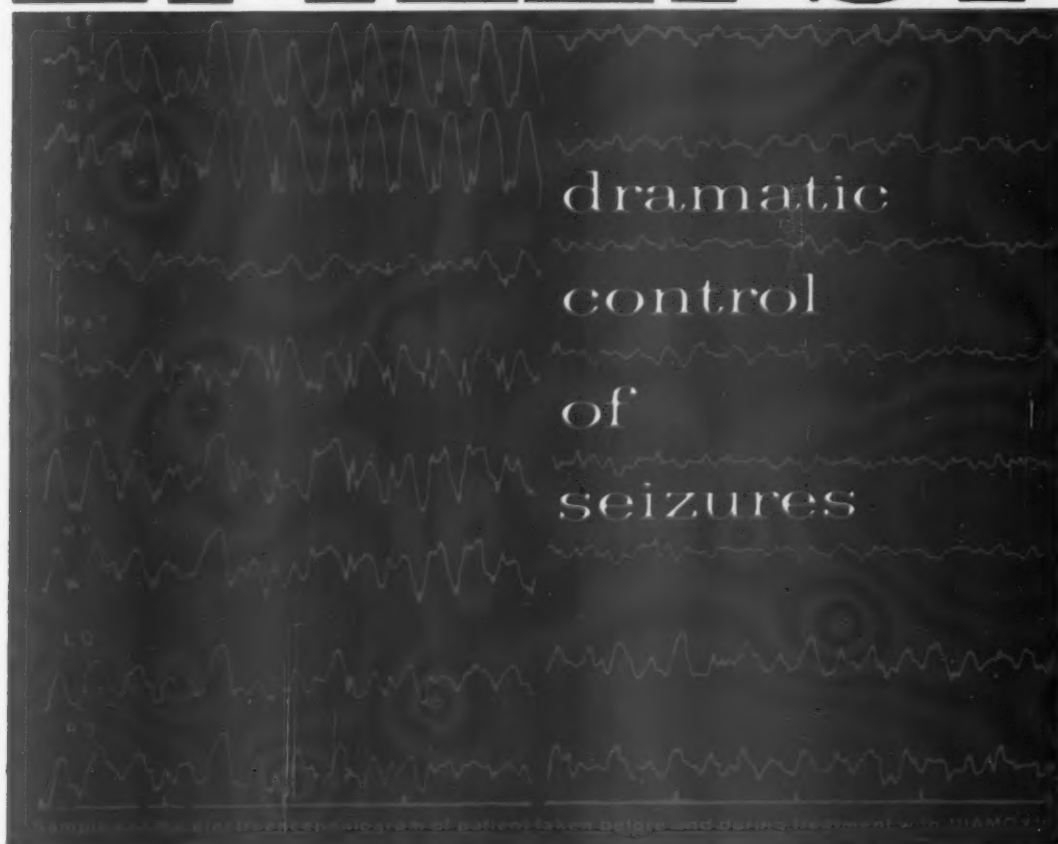
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MYSTECLIN-V PREVENTS MONILIAL OVERGROWTH



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Administered by mouth to 126 patients with various forms of epilepsy, many of whom were refractory to standard therapy, DIAMOX gave practically complete control of seizures in 34 cases, 90-99% reduction of seizures in an additional 12 cases, 50-90% in 22 cases, less than 50% in 58 cases. Diet was not restricted. *In at least half of the patients benefited, DIAMOX was used alone.*

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Measures having a beneficial influence on

epileptic seizures often involve certain drawbacks. In contrast, DIAMOX is simple to administer, has a wide margin of safety, produces a smaller systemic acidosis, has *an effect that is surprisingly well-sustained.*

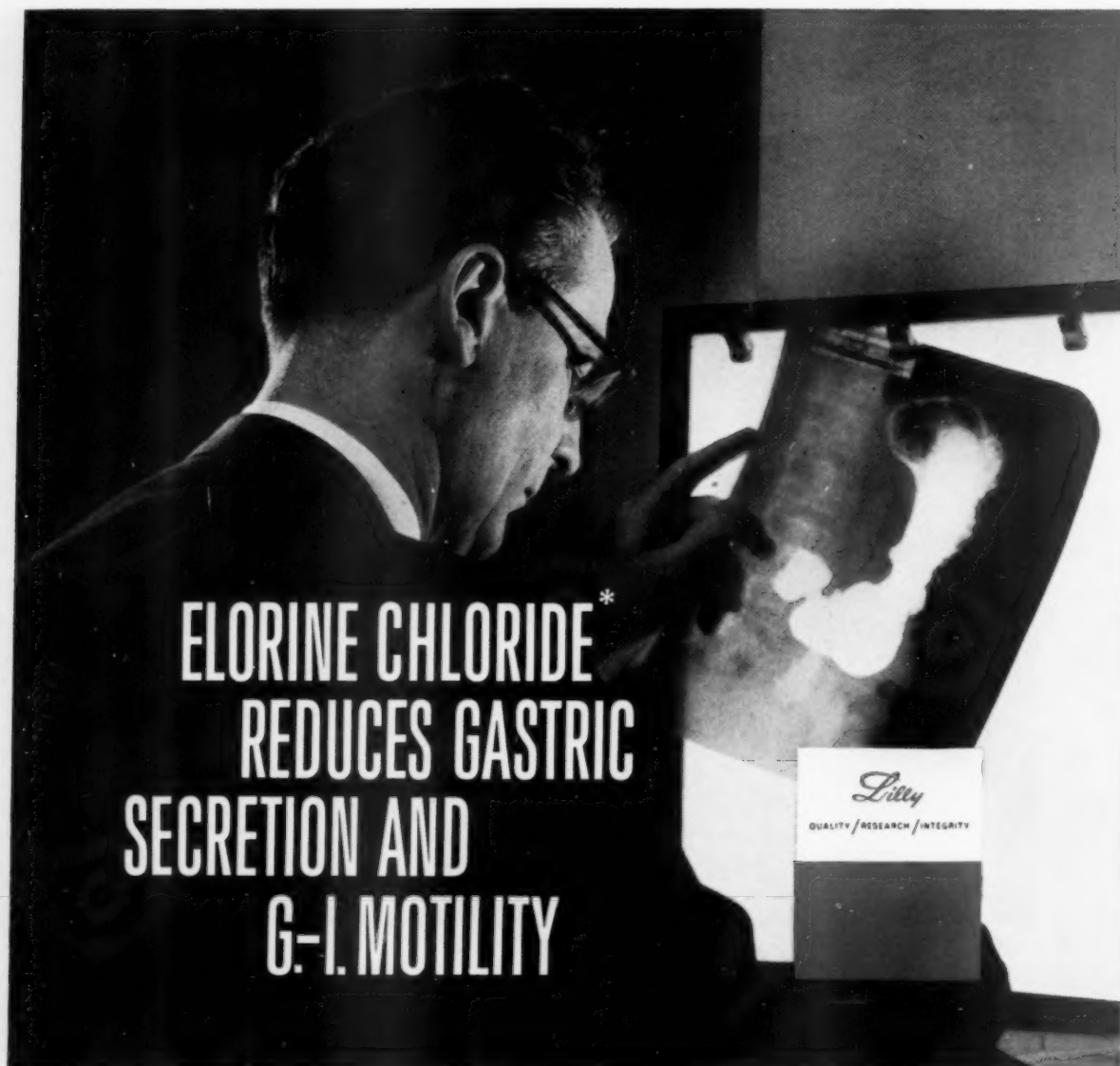
A highly versatile drug, DIAMOX has also proved singularly useful in other conditions, including cardiac edema, acute glaucoma, obesity, premenstrual tension, toxemias and edema of pregnancy.

Supplied: Scored tablets of 250 mg., Syrup containing 250 mg. per 5 cc. teaspoonful.

I. Lombroso, C. T., Davidson Jr., D. T., and Grossi-Bianchi, M. L.: Further Evaluation of Acetazolamide (DIAMOX) in Treatment of Epilepsy, J.A.M.A. 160 268-272, 1956.

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**ELORINE CHLORIDE^{*}
REDUCES GASTRIC
SECRETION AND
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Especially valuable in the management of peptic ulcer patients

The selective anticholinergic action of 'Elorine Chloride' has been shown to produce a "pronounced and significant" decrease in mean gastric volume, free and total acid, and pepsin output.¹ It also effectively reduces hypermotility of the gastro-intestinal tract (except the esophagus). Other conditions in which 'Elorine Chloride' is valuable include functional digestive disorders, acute

pancreatitis, diverticulitis, pylorospasm, and excessive sweating.

Dosage should be tailored to patient tolerance. In peptic ulcer, the average adult dose ranges from 100 to 250 mg. three or four times daily. 'Elorine Chloride' is available in pulvules of 50 and 100 mg.

^{**}'Elorine Chloride' (Tricyclamol Chloride, Lilly)

1. Sun, D. C. H., and Shay, H.: A.M.A. Arch. Int. Med., 97:442, 1956.

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The American Journal of Medicine

VOL. XXIV

FEBRUARY, 1958

No. 2

Editorial

The Milk-Alkali Syndrome

Hypercalcemia, Alkalosis and Temporary Renal Insufficiency during Milk-Antacid Therapy for Peptic Ulcer

THE syndrome of alkalosis complicating the treatment of peptic ulcer has been known for more than thirty years [1-3]. Clinical and chemical observations have defined at least two etiologic factors: (1) the excessive ingestion of soluble alkali (sodium bicarbonate) in the presence of impaired renal function, and (2) the excessive loss of gastric contents in vomiting or aspiration, typified by a decreased serum chloride and by a reciprocal increase in the serum bicarbonate content [4]. In 1936 Cope [5] described an elevation of the serum calcium and magnesium with a concomitantly increased serum bicarbonate, decreased serum chloride, elevated blood urea nitrogen and temporary impairment of renal function in four patients with peptic ulcer who were given alkalis. In 1949 Burnett and his co-workers [6] described a

syndrome in six patients with peptic ulcer who had taken large amounts of milk and soluble alkali (sodium bicarbonate) for long periods. There was associated azotemia, severe renal insufficiency, mild alkalosis and calcinosis, manifested especially by calcium deposits in the cornea. The serum phosphorus and alkaline phosphatase were normal or slightly elevated. There was no hypercalcuria; three patients died of probable renal insufficiency. Case reports subsequently have confirmed the occasional development of this syndrome in patients with peptic ulcer, taking milk and antacids; in several patients the intake of alkali was small and the intake of milk was excessive [7-17].

¹ HARDT, L. L. and RIVERS, A. B. Toxic manifestations following the alkaline treatment of peptic ulcers. *Arch. Int. Med.*, 31: 171, 1923.

² KIRSNER, J. B. and PALMER, W. L. Alkalosis complicating the Sippy treatment of peptic ulcer. *Arch. Int. Med.*, 69: 789, 1942.

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⁵ COPE, C. L. Base changes in the alkalosis produced by the treatment of gastric ulcer with alkalis. *Clin. Sc.*, 2: 287, 1936.

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A review of approximately 3,300 patients hospitalized at the University of Chicago for the management of peptic ulcer during the decade 1947 to 1956 recently has disclosed thirty-five patients with unequivocal evidence of the milk-alkali syndrome [18]. The distribution of the cases is of interest; whereas one to three instances were observed each year between 1947 and 1953, there were eight patients with the syndrome in 1954, nine during 1955 and eight during 1956. The changing incidence cannot be ascribed to a significant modification of the treatment of peptic ulcer. Therapy always has been directed towards effective, continuous neutralization of the gastric contents; calcium carbonate has been the standard antacid since 1940 but it is of interest that antacids containing aluminum hydroxide and magnesium trisilicate have been utilized more often in the past three years than formerly. Nor can the apparently increasing incidence of the syndrome be ascribed primarily to lack of awareness of the possibility of hypercalcemia. Nevertheless, in the absence of a more satisfactory explanation, the increased incidence of hypercalcemia may be related to more frequent measurements of the serum calcium. Whereas nausea in the past may have been attributed to the excessive intake of milk and cream, in recent years nausea has constituted an almost immediate indication for measurement of the serum calcium, phosphorus and other chemical constituents.

The milk-alkali syndrome may develop within several days to several weeks after the start of therapy with calcium carbonate, milk and cream, the interval averaging one week. The serum calcium may rise to maximum levels of 18 mg. per 100 ml. although the mean elevation

in our series was 14.7 mg. per 100 ml. Mild or moderately severe alkalosis is invariably present; the mean serum bicarbonate content was 38.2 mEq./L. The blood urea nitrogen is elevated and renal function is impaired temporarily. These abnormalities disappear when the antacid and milk and cream are discontinued. It is noteworthy that recovery occurred promptly in four cases, despite the continued intake of calcium carbonate, following the administration of increased amounts of salt by mouth or of isotonic saline solution and ammonium chloride intravenously. In one patient recovery followed the simple expedient of increasing the intake of water orally. In contrast, in two patients who had recovered from the acute syndrome a chemical recurrence developed within three days after resumption of the antacid program, without added salt or water. These observations appear to emphasize the importance of electrolyte and fluid balance, and especially the role of the kidneys, in the development of the syndrome. The additional sodium chloride, ammonium chloride and water presumably replace water and electrolyte loss and improve renal hemodynamics and renal function. The importance of the kidneys in the development of this syndrome is emphasized further by the fact that excessive vomiting or the aspiration of large amounts of gastric content had preceded the complication in fifteen of the thirty-five patients in our series. Gastrointestinal bleeding had occurred in eight patients; the temporary impairment of renal function accompanying hypochloremia and dehydration and gastrointestinal bleeding is well known. Pre-existing renal disease or hypertension had been present in sixteen patients although the hypertension was mild and transient in several of these. Only in one patient was there an absence of a possible predisposing factor and in this instance there was a past history of scarlet fever.

The milk-alkali syndrome is a potentially serious complication. The usual symptoms are nausea, vomiting, anorexia, weakness, headache and dizziness but mental confusion, ataxia, stupor and toxic psychosis may dominate the clinical picture. The spinal fluid protein was elevated in the one case so examined. In six of our patients deposition of calcium salts was noted in the cornea or conjunctiva; in two the changes disappeared subsequently. Renal calculi were present in two patients prior to the antacid therapy and hypercalcemia. The possibility of

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an associated primary hyperparathyroidism has been an intriguing and difficult problem, especially since hyperparathyroidism and duodenal ulcer are not infrequently associated. Clinical and chemical observations and the subsequent course have not established such a relationship. The syndrome differs from primary hyperparathyroidism in the following features: alkalosis in the presence of hypercalcemia, lack of hypophosphatemia early in the disease, lack of hypercalciuria, lowering of the serum calcium with a low calcium intake, and absence of skeletal demineralization. Nevertheless, the possibility cannot yet be excluded completely, at least in individual cases. Fortunately, no permanent abnormalities have been demonstrated following the syndrome, at least in our series; there is no evidence of permanent renal damage.

The exact mechanism of the hypercalcemia is not known and deserves further study. The present observations direct attention to the important role of the kidneys in the development of this complication. Thus in patients with pre-

existing renal disease or in those who have been vomiting or who have bled it may be desirable to discontinue or avoid calcium carbonate and milk temporarily. With the correction of these complications there would appear to be no significant hazard in the resumption of calcium carbonate. Indeed, several patients following recovery from hypercalcemia have continued the use of calcium carbonate and milk and cream without difficulty for long periods. The clinical observations also indicate the importance of measuring the serum electrolytes when nausea, distaste for food or headache develop during milk and antacid therapy. Early recognition of the milk-alkali syndrome should lead to prompt correction of the chemical disorder.

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Clinical Studies

The Vascular Status of a Heterogeneous Group of Patients with Hypertension, with Particular Emphasis on Renal Function*

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THAT hypertension produces vascular damage and that this process can be arrested by appropriate antihypertensive therapy is a hypothesis worthy of testing. Tissue injury associated with hypertensive vascular disease is found most frequently in the brain, the heart and the kidneys. The frequent coexistence of renal disease and hypertension has long been known, and the relationship between the kidney and hypertension has been a great stimulus for experimental and clinical investigation. The experimental work of Goldblatt and his associates [7], in which permanent hypertension was produced in animals by partial constriction of the renal arteries, provided laboratory evidence for a renal origin of hypertension. Contrariwise, evidence is accumulating to indicate that severe hypertension may produce renal damage. Since the introduction by Smith and his associates [2] of clearance technics for estimating renal function, the renal status of patients with hypertension has been more precisely observed [3-6]. There has been general agreement that there is a reduction in the effective renal blood flow and glomerular rate in patients with essential hypertension. Chasis and Redish [7] measured the effective renal blood flow in the separate kidneys of subjects with essential hypertension and found that the reduction in function was bilateral. Talbott and his associates [8] obtained renal biopsies in a group of patients with hypertension and were able to correlate microscopic evidence

of increased renal vascular involvement with the decrease in renal function.

We have recently completed a study of 133 hypertensive patients in whom the renal functional status was determined by means of clearance studies. The data have been analyzed in an attempt to establish the correlation, if any, between the incidence and severity of depressed renal function and the degree of blood pressure elevation. In addition, a comparison has been made between the incidence and severity of renal functional alterations and complications of hypertension in other vascular beds such as the brain and heart. The influence of factors such as age, sex and race in this group of patients has also been analyzed.

METHODS

This study consisted of a group of 133 patients, picked at random, who were among 1,100 patients treated at the Hypertensive Clinics of the Jefferson Davis (City-County) and Veterans Administration Hospitals over a six-year period, i.e., from 1951 to 1956. The patients, although picked at random from this group for renal clearance studies, are selected in that the majority of patients referred to the clinics had moderate to severe hypertension. All patients had a sustained elevation of the blood pressure above 150/100 mm. Hg in both the supine and upright positions during an initial control observation period of three to four weeks while receiving placebo therapy. Patients with evidence of primary renal disease were not included in the study. Patients with obvious clini-

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TABLE I
VITAL STATISTICS AND COMPLICATIONS IN HYPERTENSIVE PATIENTS

Data	Values	Complications	No. of Patients	%
Total no. of patients.....	133	Abnormal urine.....	72	54
Average age (yr.).....	49	Abnormal electrocardiogram.....	99	74
Age range (yr.).....	26-72	Abnormal x-ray*.....	80	60
Men.....	73	Previous infarctions (myocardial)...	3	2
Women.....	60	Previous cerebrovascular accident...	26	20
White.....	44	Funduscopy†		
Negro.....	89	Grade 1 and 2.....	76	57
Average systolic and diastolic blood pressure		Grade 3 and 4.....	52	39
Supine.....	217/132 mm. Hg	Heart failure‡		
Upright.....	213/135 mm. Hg	Class I.....	27	20
Average blood urea nitrogen, (mg. %) (R, §		Class II.....	27	20
3-216).....	27	Class III.....	18	14
Average glomerular filtration rate, (cc./min.)		Class IV.....	4	3
(R, 9-155).....	80			
Average renal blood flow, (cc./min.) (R,				
42-1706).....	743			

* = Refers to abnormalities of heart only.

† = Keith-Wagener-Barker classification.

‡ = Classification of American Heart Association.

§ = Range of values.

cal manifestations of uremia also were excluded from the study, irrespective of the cause of the renal failure.

On the initial visit to the clinic a complete history was obtained and physical examination was performed. In addition, certain routine laboratory examinations were obtained, including a complete blood count, urinalysis, blood urea nitrogen, electrocardiogram and a roentgenogram of the chest. Each patient was started on placebo medication, and blood pressure determinations were made with the patients in both the supine and upright positions once or twice a week for a period of three to four weeks. Renal function studies were performed during this observation period and consisted of determinations of the glomerular filtration rate by the inulin clearance method, and renal plasma flow by the clearance of paraaminohippuric acid. The renal blood flow was calculated from the renal plasma flow. The technic and analytical procedures of the clearance tests have been described previously [9,10]. A urinalysis and a blood urea nitrogen determination were performed prior to beginning the clearance tests and are presented in this study.

Table I presents a summary of the vital statistics and complications of hypertension in the 133 subjects of this study. In Table II the patients are analyzed and divided into subgroups on the basis of the diastolic blood pressure while in the upright position. In Table III the patients have been subgrouped on the basis of the initial glomerular filtration rate. In Tables IV and V the patients have been analyzed to determine the relationship of race and sex in the

disease process. Thirty-two of the 133 patients studied had malignant hypertension. The vital statistics, renal functional status and complications of hypertension in these patients, have been analyzed separately and are presented in Table VI.

RESULTS

The average age for the group of 133 patients was forty-nine years with a range of twenty-six to seventy-two years. (Table I.) There were seventy-three men and sixty women. Eighty-nine (67 per cent) of the patients were Negro and forty-four (33 per cent) were white. This difference is attributable to the fact that the city-county hospital serves an indigent population which in this area is comprised predominantly of the Negro race. The average blood urea nitrogen (BUN) for the group was 27 mg. per cent with a range of 3 to 216 mg. per cent. The average glomerular filtration rate was 80 cc./minute with a range of 9 to 155 cc./minute (Fig. 1) and the renal blood flow was 743 cc./minute with a range of 42 to 1,706 cc./minute. The average renal clearance values of the entire group are considerably lower than the values in normal people. (Fig. 2.) Fifty-four per cent of the patients had abnormal urine findings, 74 per cent had abnormal electrocardiograms and 60 per cent had an increased heart size by

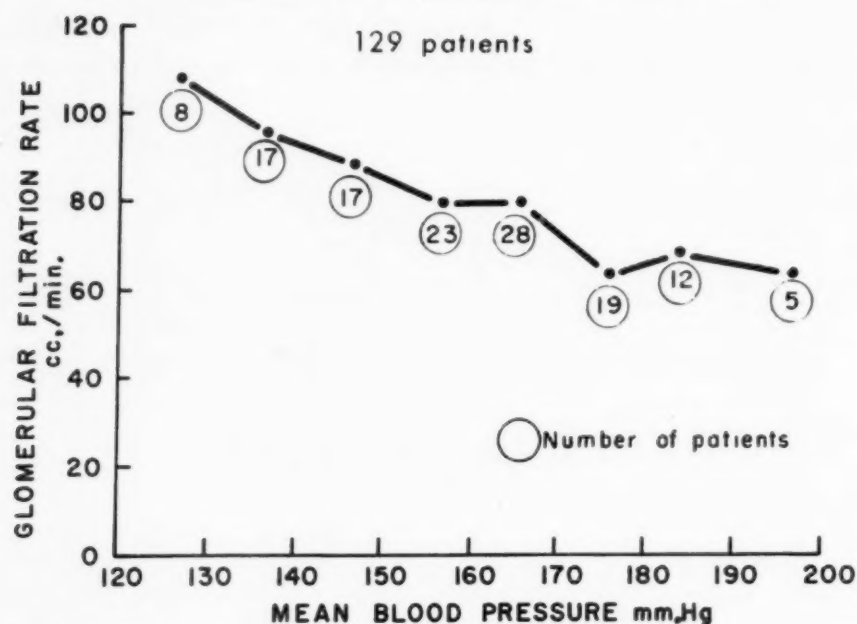


FIG. 1. The average values for glomerular filtration rate compared to increasing severity of hypertension as estimated by mean blood pressure. There is a greater reduction in glomerular filtration rate in those patients who show the greatest increase in blood pressure, thus indicating a direct relationship between the severity of the hypertension and the renal vascular deterioration.

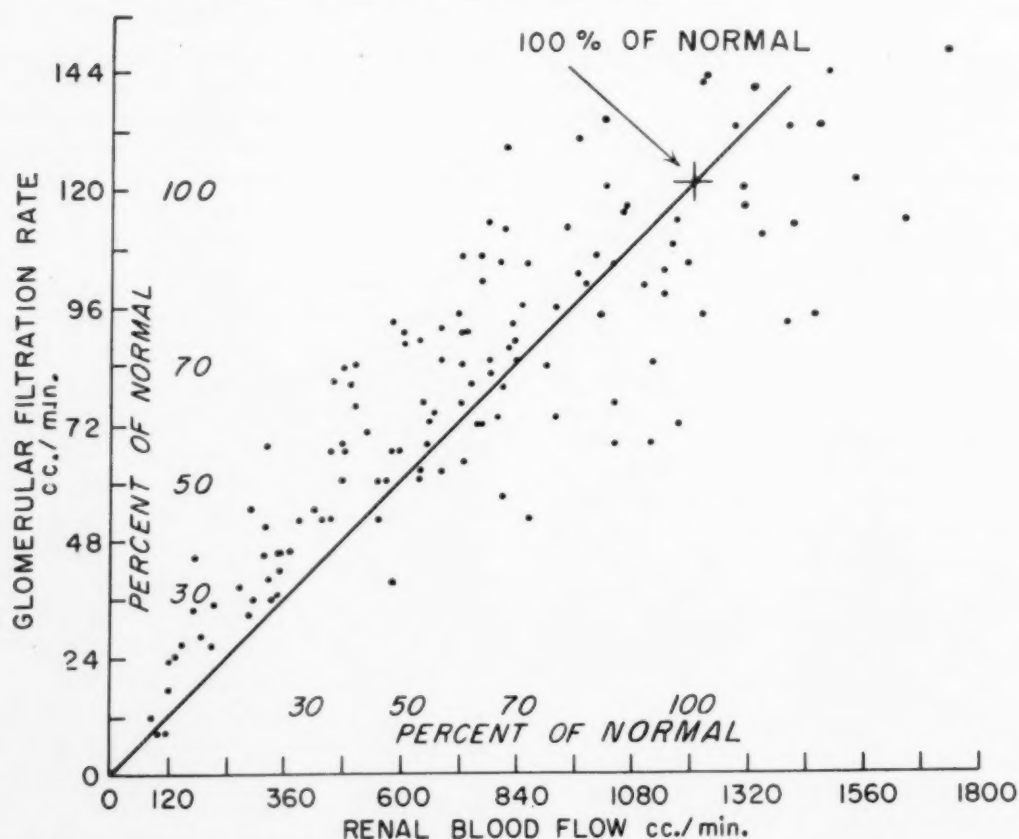


FIG. 2. Glomerular filtration rate plotted against renal blood flow (PAH clearance) (expressed as per cent of normal) in patients with hypertension. Renal blood flow, as reflected in PAH clearance, appears to be slightly more depressed than glomerular filtration rate as reflected in inulin clearance. This may be due in part to decreased extraction of PAH. The directional changes indicate a parallel reduction in glomerular filtration rate and renal blood flow with progressive renal damage.

TABLE II A
VITAL STATISTICS AND RENAL FUNCTION ON BASIS OF DIASTOLIC BLOOD PRESSURE

Data	Diastolic Blood Pressure			Total
	Subgroup A (100 to 120 mm. Hg)	Subgroup B (121 to 140 mm. Hg)	Subgroup C (above 140 mm. Hg)	
No. of patients.....	34	55	44	133
Per cent of total patients.....	26	41	33	100
Average age (yr.).....	49	50	48	49
Men.....	17	28	28	73
Women.....	17	27	16	60
White.....	6	13	25	44
Negro.....	28	42	19	89
Blood pressure, supine				
Average systolic.....	190	217	238	217
Average diastolic.....	113	129	151	132
Average mean*.....	139	158	180	160
Blood pressure, upright				
Average systolic.....	187	214	232	213
Average diastolic.....	114	132	153	135
Average mean*.....	138	159	179	161
Average blood urea nitrogen, (mg. %). . .	23	24	33	27
Average glomerular filtration rate, (cc./min.) . . .	92	83	66	80
Average renal blood flow, (cc./min.) . . .	927	757	575	743

* = Diastolic + $\frac{1}{3}$ pulse pressure.

TABLE II B
COMPLICATIONS OF HYPERTENSION DIVIDED ON BASIS OF DIASTOLIC BLOOD PRESSURE

Data	Diastolic Blood Pressure						Total	
	Subgroup A (100 to 120 mm. Hg)		Subgroup B (121 to 140 mm. Hg)		Subgroup C (above 140 mm. Hg)			
	No.	%	No.	%	No.	%	No.	%
Patients.....	34	..	55	..	44	..	133	..
Abnormal urine.....	10	29	25	45	37	84	72	54
Abnormal electrocardiogram.....	26	76	34	62	39	89	99	74
Abnormal x-ray.....	14	41	30	55	36	82	80	60
Previous infarction.....	1	3	0	0	2	5	3	2
Previous cerebrovascular accident.....	3	9	11	20	12	27	26	20
Funduscopy								
Grade 1 and 2.....	26	76	36	65	14	32	76	57
Grade 3 and 4.....	5	15	17	31	30	68	52	39
Heart failure								
Class I.....	5	15	18	33	4	9	27	20
Class II.....	9	26	11	20	7	16	27	20
Class III.....	3	9	6	11	9	20	18	14
Class IV.....	1	3	2	4	1	2	4	3

roentgenogram of the chest. Two per cent of the patients had had previous myocardial infarctions and 20 per cent had had previous cerebral vascular accidents. Only current electrocardiographic changes or other incontrovertible evidence was accepted as indicative of a previous myocardial infarction. An undocumented history alone was not accepted. There was a high incidence of cerebral vascular involvement in these patients, but episodes of encephalopathy were purposely excluded from the analyses of this data because of the difficulty in establishing the true incidence of occurrence. Fifty-seven per cent of the patients had grades 1 and 2 funduscopic changes and 39 per cent had grade 3 and 4 changes. Fifty-seven per cent of the patients manifested signs and symptoms of heart failure, varying from minimal to class iv. The average supine and upright blood pressures for the group were 217/132 mm. Hg and 213/135 mm. Hg, respectively.

In Tables II A and II B the patients have been divided into subgroups on the basis of the upright diastolic blood pressure. Subgroup A contains thirty-four patients with a sustained diastolic pressure of 100 to 120 mm. Hg. The average BUN was 23 mg. per cent, the glomerular filtration rate 92 cc./minute and the renal blood flow 927 cc./minute (Table II A). In subgroup B (fifty-five patients with a diastolic pressure of 121 to 140 mm. Hg) the average BUN was 24 mg. per cent, the glomerular filtration rate 83 cc./minute, and the renal blood flow 757 cc./minute. In subgroup C (forty-four patients with a diastolic pressure above 140 mm. Hg) these values were 33 mg. per cent, 66 cc./minute and 575 cc./minute, respectively. Thus the diastolic pressure is inversely related to the depression of renal function. It is only after the glomerular filtration rate and the renal blood flow fall to approximately 60 to 70 per cent of the normal values (subgroup C) or below, that the BUN reaches abnormal levels. (Fig. 3.) The results summarized in Table II B show that, in general, the higher the diastolic blood pressure, the higher the incidence of complications associated with hypertension. This relationship is particularly noteworthy in the roentgenographic changes indicating cardiomegaly, the incidence of cerebrovascular accidents, the incidence of grades 3 and 4 eyeground changes and the incidence of abnormal findings in the urine. The incidence of electrocardiographic changes and heart fail-

ure did not appear to be closely related to the degree of diastolic blood pressure elevation.

In Tables III A and III B the patients are divided into subgroups on the basis of the glomerular filtration rate at the time of study. Subgroup I contains thirty-nine patients (29 per cent of the total) with a glomerular filtration rate of 100 cc./minute or more, which could be considered normal. The average BUN for this group was 15 mg. per cent, the average glomerular filtration rate was 118 cc./minute, the average renal blood flow was 1,111 cc./minute; all of these values are normal. The average upright blood pressure for this subgroup was 200/129 mm. Hg with a mean blood pressure of 153 mm. Hg. In subgroup II (twenty-nine patients with a glomerular filtration rate of 80 to 99 cc./minute) the average values were 17 mg. per cent for the BUN, 89 cc./minute for the glomerular filtration rate, 809 cc./minute for the renal blood flow and 156 mm. Hg for the mean blood pressure. Thus the crude average blood pressure for this group with minimal depression of renal function was approximately the same as it was for the patients in group I with entirely normal renal function. The corresponding values in subgroup III (glomerular filtration rate 40 to 79 cc./minute) were BUN 25 mg. per cent, glomerular filtration rate 62 cc./minute, renal blood flow 593 cc./minute and mean blood pressure 169 mm. Hg, indicating a more severe hypertension associated with the depressed renal function. In subgroup IV (glomerular filtration rate below 40 cc./minute) the average BUN was 72 mg. per cent with a glomerular filtration rate of 27 cc./minute, a renal blood flow of 212 cc./minute and a mean blood pressure of 169 mm. Hg. The duration of the hypertensive vascular disease was not taken into account in the analysis of these data.

The apparent difference between the elevated BUN of 33 mg. per cent in subgroup C in Table II A and a normal BUN of 25 mg. per cent in subgroup III in Table III A, arises from the fact that in the former group the patients are divided according to blood pressure elevation and contain patients with normal to severely depressed renal functions, whereas in the latter group the patients are divided on the basis of the glomerular filtration rate. The duration of the blood pressure elevation is, no doubt, an important consideration in determining the degree of renal damage present at any specific time in the natural history of the disease. Unfortunately, it

TABLE IIIA
COMPARISON ON BASIS OF INITIAL GLOMERULAR FILTRATION RATE

Data	Glomerular Filtration Rate (cc./min.)				Total
	Subgroup I (above 100)	Subgroup II (80 to 99)	Subgroup III (40 to 79)	Subgroup IV (below 40)	
No. of patients.....	39	29	48	17	133
Per cent of total patients.....	29	22	36	13	100
Average age (yr.).....	48	51	50	48	49
Men.....	20	12	28	13	73
Women.....	19	17	20	4	60
White.....	12	7	16	9	44
Negro.....	27	22	32	8	89
Blood pressure, supine					
Average systolic.....	203	214	228	222	217
Average diastolic.....	125	131	138	139	132
Average mean.....	151	159	168	167	160
Blood pressure, upright					
Average systolic.....	200	205	226	221	213
Average diastolic.....	129	131	141	143	135
Average mean.....	153	156	169	169	161
Average blood urea nitrogen, (mg. %).....	15	17	25	72	27
Average glomerular filtration rate, (cc./min.)....	118	89	62	27	80
Average renal blood flow, (cc./min.).....	1111	809	593	212	743

TABLE IIIB
COMPARISON OF COMPLICATIONS OF HYPERTENSION DIVIDED ON BASIS OF
INITIAL GLOMERULAR FILTRATION RATE

Data	Glomerular Filtration Rate (cc./min.)								Total	
	Subgroup I (above 100)		Subgroup II (80 to 99)		Subgroup III (40 to 79)		Subgroup IV (below 40)			
	No.	%	No.	%	No.	%	No.	%	No.	%
Patients.....	39	..	29	..	48	..	17	..	133	..
Abnormal urine.....	14	36	16	55	29	60	13	76	72	54
Abnormal electrocardiogram.....	26	67	21	72	37	77	15	88	99	74
Abnormal x-ray.....	19	49	19	66	29	60	13	76	80	60
Previous infarction.....	0	0	1	3	2	4	0	0	3	2
Previous cerebrovascular accident.....	6	15	5	17	11	23	4	24	26	20
Funduscopy										
Grade 1 and 2.....	24	62	21	72	24	50	7	41	76	57
Grade 3 and 4.....	12	31	8	28	22	46	10	59	52	39
Heart failure										
Class I.....	11	28	9	31	6	13	1	6	27	20
Class II.....	8	21	5	17	8	17	6	35	27	20
Class III.....	3	8	6	21	7	15	2	12	18	14
Class IV.....	0	0	1	3	2	4	1	6	4	3

TABLE IV A
COMPARISON OF RENAL STATUS IN HYPERTENSIVE PATIENTS OF VARIOUS AGE GROUPS

Data	Subgroup 1 (to age 40)	Subgroup 2 (41-55)	Subgroup 3 (above age 55)	Total
No. of patients	28	67	38	133
Per cent of total patients	21	50	29	100
Average age (yr.)	35	48	61	49
Men	14	36	23	73
Women	14	31	15	60
White	10	23	11	44
Negro	18	44	27	89
Blood pressure, supine				
Average systolic	206	218	223	217
Average diastolic	136	132	129	132
Average mean	159	161	160	160
Blood pressure, upright				
Average systolic	203	211	223	213
Average diastolic	139	135	132	135
Average mean	160	160	162	161
Average blood urea nitrogen, (mg. %)	25	27	28	27
Average glomerular filtration rate, (cc./min.)	85	78	80	80
Average renal blood flow, (cc./min.)	774	754	703	743

TABLE IV B
COMPLICATIONS OF HYPERTENSION IN VARIOUS AGE GROUPS

Data	Subgroup 1 (to age 40)		Subgroup 2 (41-55)		Subgroup 3 (above age 55)		Total	
	No.	%	No.	%	No.	%	No.	%
Patients	28	..	67	..	38	..	133	..
Abnormal urine	16	57	36	54	20	53	72	54
Abnormal electrocardiogram	18	64	51	76	30	79	99	74
Abnormal x-ray	14	50	40	60	26	68	80	60
Previous infarction	0	0	1	1	2	5	3	2
Previous cerebrovascular accident	3	11	13	19	10	26	26	20
Funduscopy								
Grade 1 and 2	13	46	38	57	25	66	76	57
Grade 3 and 4	14	50	28	42	10	26	52	39
Heart failure								
Class I	4	14	15	22	8	21	27	20
Class II	7	25	16	24	4	11	27	20
Class III	2	7	9	13	7	18	18	14
Class IV	0	0	3	4	1	3	4	3

was impossible to determine the duration of disease in these patients. The observations recorded in Table III A again emphasize that these indices of renal function may be depressed to approximately 60 to 70 per cent of normal without producing an increase in blood urea nitrogen. A progressive rise in mean blood pressure can be correlated with a fall in the glomeru-

lar filtration rate, and renal blood flow, and an elevation of the blood urea nitrogen. The results given in Table III B show that there is a greater incidence of complications of hypertension as the glomerular filtration rate and renal blood flow are reduced, indicating increasing generalized vascular involvement. It would appear that the glomerular filtration rate is a fair indication

TABLE vA
COMPARISON OF RENAL STATUS IN HYPERTENSIVE PATIENTS BASED ON SEX AND RACE

Sex	No.	%	Age (yr.)	Blood Urea Nitrogen (mg. %)	Glomerular Filtration Rate (cc./min.)	Renal Blood Flow (cc./min.)	Control Blood Pressure					
							Supine			Upright		
							S	D	M	S	D	M
I. Men												
A. Negro.....	41	56	52	31	77	715	212	130	157	210	132	158
B. White.....	32	44	48	32	73	662	227	145	172	218	146	170
Total A + B....	73	55	50	31	75	691	218	136	163	213	138	163
II. Women												
A. Negro.....	48	80	48	19	88	813	210	126	154	209	130	156
B. White.....	12	20	51	28	76	752	235	136	169	228	142	171
Total A + B....	60	45	49	21	85	801	215	128	157	213	132	159
Total I + II.....	133		49	27	80	743	217	132	160	213	135	161
Race												
Negro.....	89	67	50	25	83	769	211	127	155	209	131	157
White.....	44	33	49	31	74	686	229	142	171	220	144	169

NOTE: S = Systolic blood pressure.

D = Diastolic blood pressure.

M = Mean blood pressure (diastolic + $\frac{1}{3}$ pulse pressure).

TABLE vB
COMPARISON OF COMPLICATIONS IN HYPERTENSIVE PATIENTS BASED ON SEX AND RACE

Data	Subgroup I—Men				Subgroup II—Women				Total	
	Negro		White		Negro		White		No.	%
	No.	%	No.	%	No.	%	No.	%		
Patients.....	41	..	32	..	48	..	12	..	133	..
Abnormal urine.....	20	49	21	66	25	52	6	50	72	54
Abnormal electrocardiogram.....	36	88	28	88	27	56	8	67	99	74
Abnormal x-ray.....	26	63	20	63	25	52	9	75	80	60
Previous infarction.....	1	2	2	6	0	0	0	0	3	2
Previous cerebrovascular accident.....	10	24	9	28	6	13	1	8	26	20
Funduscopy										
Grade 1 and 2.....	28	68	11	34	33	69	4	33	76	57
Grade 3 and 4.....	12	29	20	63	12	25	8	67	52	39
Heart failure										
Class I.....	11	27	1	3	15	31	0	0	27	20
Class II.....	6	15	7	22	10	21	4	33	27	20
Class III.....	8	20	3	9	6	13	1	8	18	14
Class IV.....	2	5	1	3	1	2	0	0	4	3

TABLE VI
VITAL STATISTICS, RENAL HEMODYNAMICS AND COMPLICATIONS IN THIRTY-TWO PATIENTS
WITH MALIGNANT HYPERTENSION

Data	Values	Complications	No. of Patients	%
Total no. of patients.....	32	Abnormal urine.....	26	81
Average age (yr.).....	44	Abnormal electrocardiogram.....	30	94
Age range (yr.).....	26-66	Abnormal x-ray.....	26	81
Men.....	20	Previous infarction.....	2	6
Women.....	12	Previous cerebrovascular accident...	5	16
White.....	20	Funduscopy		
Negro.....	12	Grade 1 and 2.....	0	0
Average systolic and diastolic blood pressure		Grade 3 and 4.....	32	100
Supine.....	239/150 mm. Hg	Heart failure		
Upright.....	233/151 mm. Hg	Class I.....	2	6
Average blood urea nitrogen, mg. % (R, 7-99).....	34	Class II.....	7	22
Average glomerular filtration rate, cc./min. (R, 18-146).....	66	Class III.....	3	9
Average renal blood flow, cc./min. (R, 118-1484).....	572	Class IV.....	2	6

of the degree of vascular deterioration that has occurred throughout the body.

In Table ivA and ivB the patients are subdivided on the basis of age. Three age groups were chosen arbitrarily and consisted of twenty-eight patients (21 per cent), age forty years or less, sixty-seven patients (50 per cent), age forty-one to fifty-five, and thirty-eight patients (29 per cent), above the age of fifty-five. The data in Table ivA show that age did not influence the renal hemodynamics in the patients studied in this series. The BUN, glomerular filtration rate, renal blood flow and mean blood pressure were almost identical in the different age groups. These results differ somewhat from those generally found by other investigators who report more advanced renal involvement in the younger patient.

The data in Table ivB show that there is a higher incidence of abnormal electrocardiographic and x-ray findings in the older age group (subgroup 3), as well as a slightly higher incidence of previous myocardial infarctions and cerebral vascular accidents. All of these findings can be explained on the basis of a higher incidence of associated arteriosclerosis occurring in the older age group. In contrast to these findings, a higher incidence of grades 3 and 4 funduscopy changes occurred in the younger age group.

In Tables vA and vB the observations are

analyzed on the basis of race and sex of the patients. There was no significant race or sex difference in the average renal function studies. The average values for all groups were below the normal range. The mean blood pressure was highest in the white men and white women as compared to the Negro patients. Also, there was a slightly higher incidence of complications of hypertension in the white male patients (Table vB).

In Table vi the vital statistics, renal hemodynamics and complications of hypertension in thirty-two patients with malignant hypertension are presented. The average age was forty-four years with a range of twenty-six to sixty-six. There were twenty men and twelve women. Twelve were Negro and twenty were white. The average BUN was 34 mg. per cent, the average glomerular filtration rate 66 cc./minute and the average renal blood flow 572 cc./minute. There was a high incidence of complications. Eighty-one per cent had abnormal urinary findings, 94 per cent had abnormal electrocardiograms and 81 per cent had abnormal heart size by x-ray examination of the chest. Six per cent of the patients had had previous myocardial infarction, and 16 per cent had had previous cerebral vascular accidents. All of the patients showed grade 4 funduscopy changes by the Keith, Wagener, Barker classification. The average blood pressure for the group was

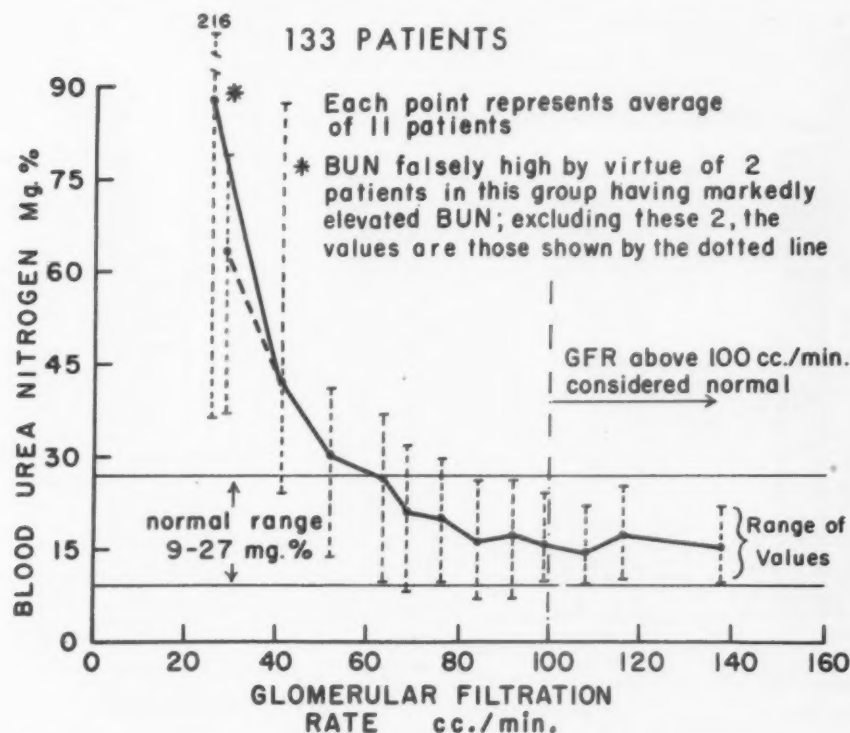


FIG. 3. Glomerular filtration rate plotted against blood urea nitrogen. Blood urea nitrogen is not elevated significantly until the glomerular filtration rate is reduced below approximately 70 cc. per minute. From this point on there is a parallel rise in blood urea nitrogen as the glomerular filtration is reduced.

239/150 mm. Hg and 233/151 mm. Hg with the patients in the supine and upright positions, respectively.

COMMENTS

The average glomerular filtration rate of 80 cc./minute and renal blood flow of 743 cc./minute for this group of patients with hypertension are below these same values of 131 cc./minute and 1,209 cc./minute, respectively, for a group of normal individuals, as reported by Smith and his associates [17]. Although the absolute figures obtained in our series differ somewhat from those reported by others [3-6], the results in general are in agreement. Not only does reduced renal function occur in patients with hypertension, but a rather definite correlation between the severity of the hypertension based upon diastolic blood pressure elevation and the degree of decreased function can be demonstrated. (Table II A.) As the diastolic pressure rises the glomerular filtration rate (Fig. 1) and renal blood flow decrease (Fig. 2), accompanied by a rising BUN. (Fig. 3.) The average values in those patients with mild elevation in blood pressure (diastolic less than 120 mm. Hg) were normal and, indeed, early renal involvement

would have escaped detection if special clearance tests had not been used. The lower incidence of complications of hypertension in this group (subgroup A, Table II B) is evidence for early though minimal generalized vascular involvement. Evidence that the disease process is one of increasing generalized vascular involvement is borne out by the patients in subgroups B and C (Table II A and II B) who show an increased incidence of complications associated with a rise in blood pressure and a fall in renal function. (Fig. 1.)

The fact that hypertension is not always accompanied by renal involvement has been shown by other investigators and has been verified in this series. The work of Talbott *et al.* [8] showed rather clearly that there were instances in which hypertension was not accompanied by changes in the renal vasculature, by means of renal biopsies in patients with hypertension. In our own series, thirty-nine patients (29 per cent) had glomerular filtration rates above 100 cc./minute, which we consider to be within the normal range. The average glomerular filtration rate for this group was 118 cc./minute with a renal blood flow of 1,111 cc./minute, both within the range of normal. The average blood

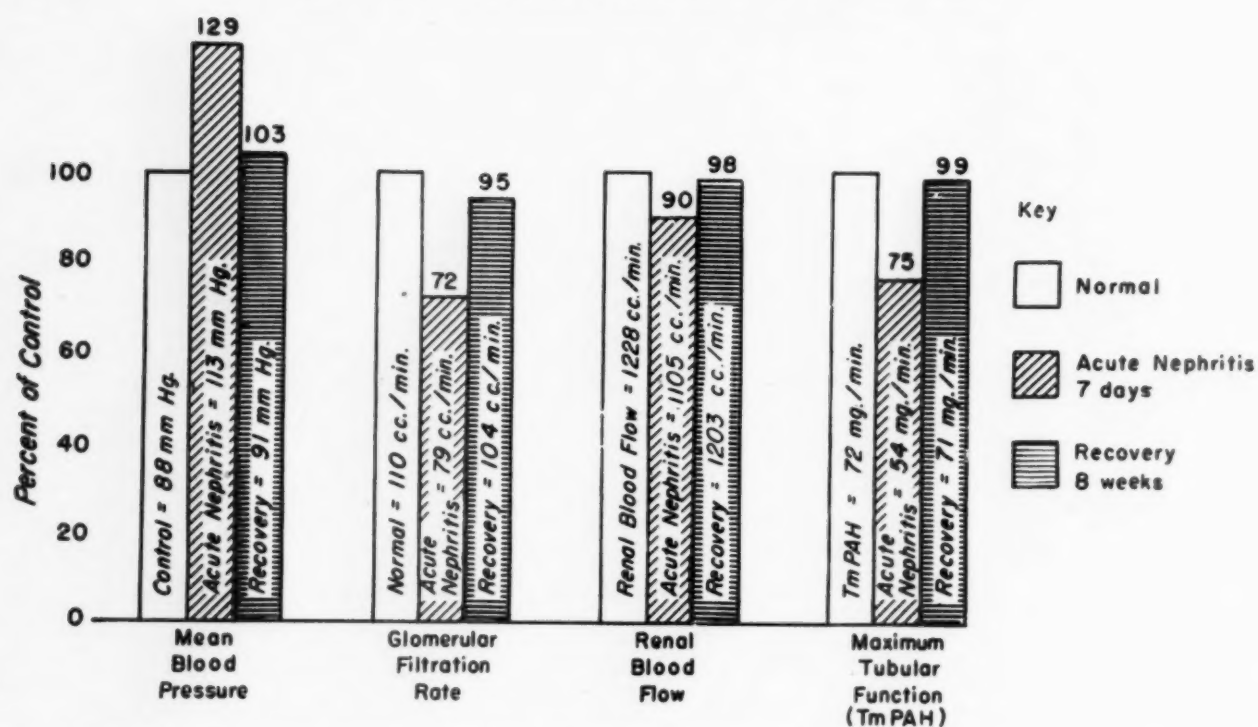


FIG. 4. Effect of acute glomerulonephritis on renal function in six patients.

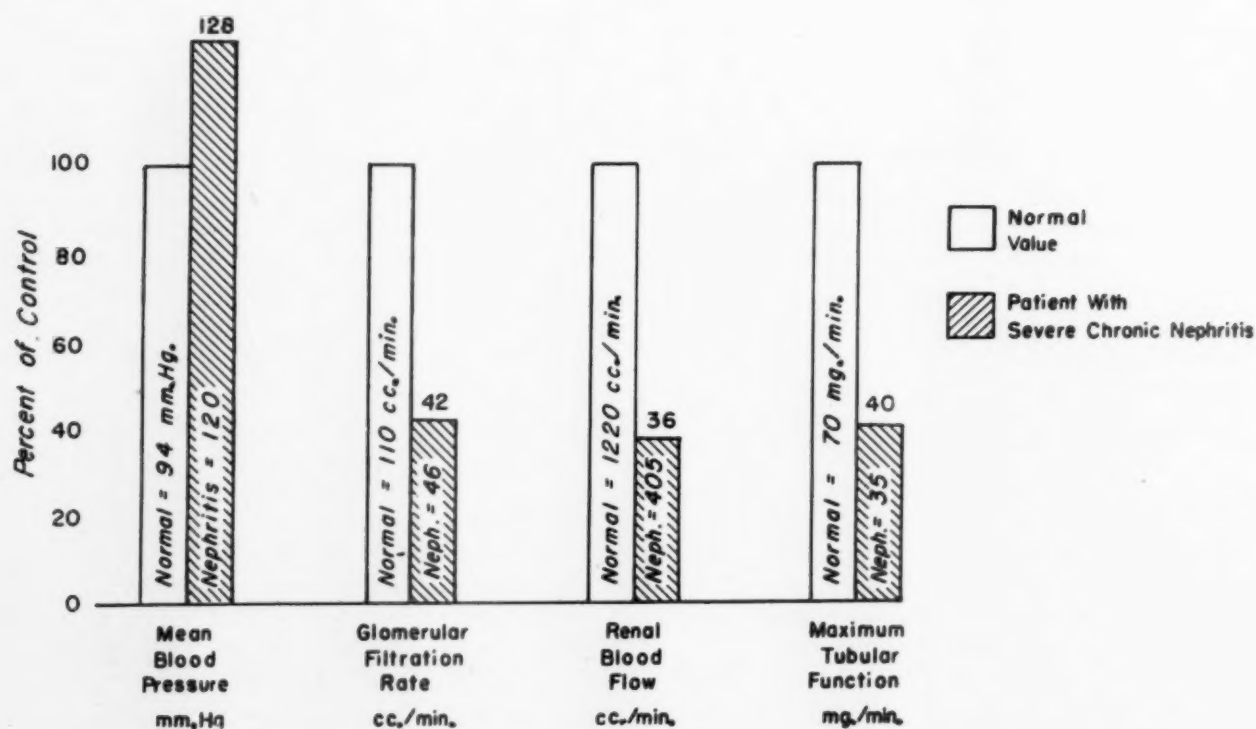


FIG. 5. Effect of advanced chronic glomerulonephritis on renal function in eight patients. The depressed renal function in these patients with primary renal disease is similar to the altered renal function seen in patients with advanced renal vascular deterioration associated with severe essential hypertension.

pressure for this group was 200/129 mm. Hg with the patient in the upright position. These results, together with Talbott's findings in renal biopsies, as well as those of others, suggest that renal deterioration is secondary to the hypertension and does not precede it. However the pattern of alteration in renal function is similar to that observed in patients with acute or chronic nephritis. (Figs. 4 and 5.)

Seventy-one per cent of the patients had definite evidence of progressive renal involvement associated with a rising blood pressure (Table IIIA), suggesting a disease process which, if not altered, has a grave prognosis. Evidence in support of this statement is presented in Table IIIB which shows that there is a definite increase in the complications of hypertension in patients who have increased renal vascular involvement as reflected in the depression in the glomerular filtration rate.

Applied clinically, these results and those of others offer evidence that benign and malignant hypertension ultimately leads to a decrease in renal function, the latter having an accelerated course. The rather clear evidence that there is a progressive decrease in function which can be correlated with an increase in blood pressure as well as an increase in complications of hypertension, suggests to us that treatment of this condition may be of value. The age at which hypertension appears, or the sex and race in which it occurs, is no contraindication to therapy, since the results (Tables IV and V) indicate that these factors have little influence on the disease process.

Since no renal involvement can be demonstrated by clearance tests or by renal biopsy in many hypertensive patients with only mild to moderate blood pressure elevation, early treatment may be of prophylactic value even though the hypertension is mild. Treatment may help to arrest or delay the process in patients with severe disease even when renal damage is present. At present the evidence to support these statements is all indirect and consequently not conclusive. Talbott and his associates [8] followed up a small number of patients who were treated surgically by sympathectomy, and their results suggested that treatment is of value. The follow-up period in patients with control observations was of rather short duration and the long-term effects will have to await further evaluation.

We have been fortunate enough to have ob-

served sixty-four of the 133 patients in this series for periods up to five years, with renal function studies. Approximately 70 per cent of the sixty-four patients have been treated medically. The others received no treatment, either as a result of lack of effective drugs at the time or because they declined to take medication for one reason or another. These results will be reported subsequently [12].

SUMMARY

The renal functional status of 133 patients with hypertension was determined by means of clearance tests. An attempt was made to correlate the renal damage (and other complications of hypertension) with the blood pressure elevation.

The results are in general agreement with those obtained by other investigators. There is a definite decrease in glomerular filtration rate and renal blood flow for the group as a whole. As the blood pressure increases there is a progressive decline in renal function and an increased incidence of complications in these patients. Age, sex and race did not appear to influence the disease process in this group of patients.

The patients with malignant hypertension tended to have greater renal damage in association with more severe generalized vascular disease.

Acknowledgments: The authors wish to acknowledge the assistance of the following investigators who have assisted in the care of the patients (reported herein) over the past six years: Drs. Edward Dennis, Warren Hughes, Robert McConn, W. R. Livesay and Robert Hershberger.

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The Effect of Treatment on the Vascular Deterioration Associated with Hypertension, with Particular Emphasis on Renal Function*

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ALTHOUGH effective reduction of the blood pressure in patients with hypertension can be readily accomplished with the use of rather recently developed drugs, the effectiveness of blood pressure reduction in arresting the vascular injury associated with hypertension has not been proved. Extensive work by numerous investigators has shown that the renal vascular system is frequently involved in the disease process. By the use of clearance tests, and by renal biopsies, it has been shown that all degrees of renal deterioration occur in patients suffering from hypertension [1-6]. We have recently completed an analysis of 133 patients with hypertensive vascular disease in which the renal functional status of the patients was determined by means of clearance tests [7]. Results of the analysis were in agreement with those previously reported by others, demonstrating that patients with hypertension have a significant reduction in glomerular filtration rate and renal blood flow which is proportional to the severity and duration of the sustained blood pressure elevation.

Clinical observations made on a few patients with malignant hypertension (Figs. 1A to 1C) suggested that blood pressure reduction was of some value in arresting the renal deterioration that occurs in patients with this disease. With this in mind, follow-up differential renal function studies were made in sixty-four of the 133 patients who had been studied in a similar manner two to five years previously. Of these, forty-five had been treated adequately for their hy-

pertension, whereas the other nineteen were untreated. This report compares the control and follow-up renal functional status in patients with hypertension before and after treatment with that group of patients in whom hypertension was not treated. Twenty-one of the patients with follow-up renal function studies had malignant hypertension, and these were further analyzed separately. Forty-four of the 133 patients originally studied by differential renal function tests have died. The incidence and causes of death have been analyzed in both the treated and untreated patients. Five additional patients with severe hypertension resulting from unilateral renal disease have also been observed before and after treatment.

METHODS

The patients with essential hypertension who were used in this study were picked at random from a group of 1,100 patients seen at the Hypertensive Clinics of the Jefferson Davis (City-County) and the Veteran's Administration Hospitals over a six-year period from 1951 to 1956. All patients had a sustained elevation of the blood pressure above 150/100 mm. Hg in both the supine and upright positions during a control observation period of three to four weeks while receiving placebo therapy. None of the patients had evidence of primary renal disease.

On the initial visit to the clinic a complete history was obtained and physical examination was performed. In addition, certain routine laboratory examinations were obtained: complete blood count, urinalysis, blood urea nitrogen determination, electrocardiogram and x-ray of the chest. Each patient

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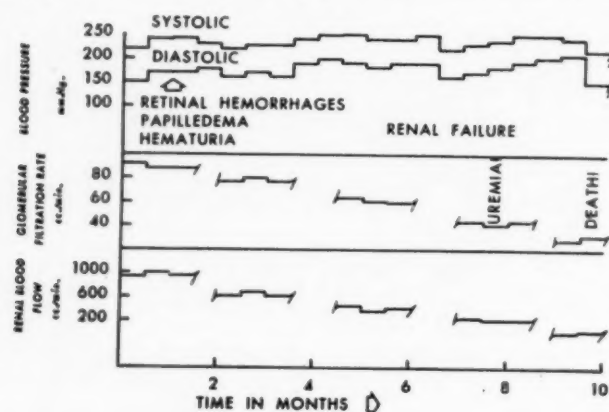


FIG. 1A. Progressive vascular deterioration observed in a patient with malignant hypertension who was not treated.

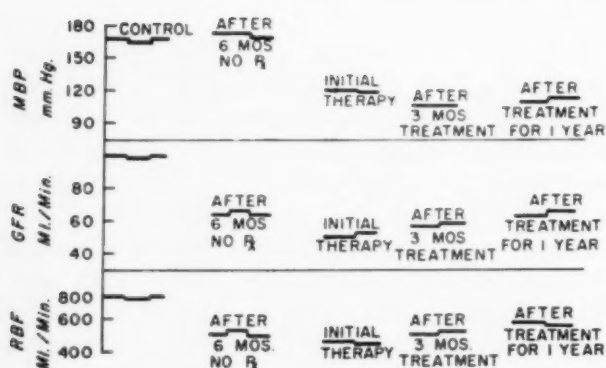


FIG. 1B. Patient with malignant hypertension showing progressive renal vascular deterioration over a period of six months without treatment. Following blood pressure reduction with rauwolfia in combination with a ganglionic blocking agent (mecamylamine), the vascular deterioration was arrested but did not return to normal after a period of one year.

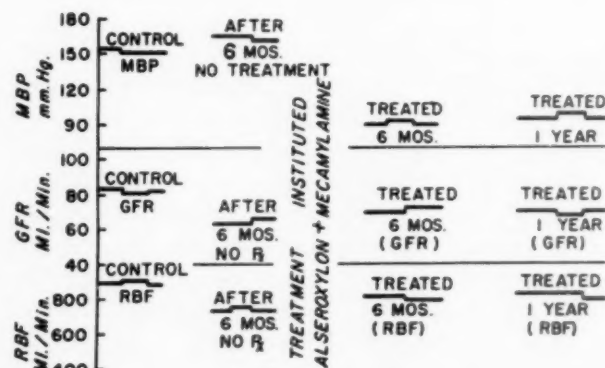


FIG. 1C. The effect of malignant hypertension on the kidney in another patient who did not receive treatment for six months. Following blood pressure reduction, vascular deterioration was arrested, but here again, renal function did not return to normal following therapy.

was started on a placebo regimen and blood pressure determinations were made with the patient in both the supine and upright positions once or twice a week for a period of three to four weeks. The glomerular filtration rate (inulin clearance) and the renal plasma flow (clearance of para-aminohippurate) were determined during this observation period. The renal blood flow was calculated from the renal plasma flow. The techniques and analytical procedures of the clearance tests have been described previously [8,9]. These observations served as control values (C) in the study. Repeated follow-up renal function studies were performed in sixty-four patients. The last follow-up observations are the ones used for analysis of data in this study and are referred to as D₁. The duration of the follow-up period (D₁) ranged from two to five years except in those patients who died in less than two years. Blood urea nitrogen determinations, electrocardiograms and x-rays of the chest were obtained immediately prior to the follow-up renal function studies and are the ones presented in this study. Forty-five of the patients obtained a significant reduction in

blood pressure throughout the follow-up period. This is defined as a reduction in the mean blood pressure (diastolic + $\frac{1}{3}$ pulse pressure) of 20 mm. Hg or more, or a return to normotensive levels. Nineteen patients had not had treatment of their hypertension, either because effective drugs were lacking at the time or because they moved from the area and did not continue therapy, or they voluntarily discontinued their medication before an effective therapeutic program was established.

In addition to the patients with "essential hypertension," five patients with unilateral vascular occlusive disease of one renal artery were studied. All five patients had severe hypertension. Nephrectomy was performed in three patients, but because of some relative contraindication two were treated medically with antihypertensive drugs only. The ureters were catheterized in these patients and glomerular filtration rate and renal blood flow determined in each kidney independently before and after therapy for the hypertension.

The antihypertensive therapy for the patients with essential hypertension varied in this study. During

1951 and 1952 therapy consisted primarily of ganglionic blockade with hexamethonium.* These patients have continued to receive a combination of rauwolfia with a ganglionic blocking agent, which during the past three years has been either pentolinium† or mecamlamine.‡ Methods and techniques employed when administering these drugs have been reported previously [10-17]. About 10 per cent of the patients in this study received a combination of rauwolfia with hydralazine§ (apresoline®) for variable periods of time. This combination was not continued because it proved inadequate for long-term blood pressure control.

RESULTS

In Tables 1A and 1B are presented the pre-treatment vital statistics, renal functional status and complications of hypertension in the sixty-four patients in whom we were able to perform follow-up renal function studies. The patients have been divided into two groups on the basis of the diastolic blood pressure elevation. Group I contains patients with mild to moderate hypertension (diastolic less than 130 mm. Hg), group II contains patients with more severe hypertension (diastolic greater than 130 mm. Hg). These groups are further subdivided into treated and untreated patients. There is no significant difference in the control renal functional status between treated and untreated patients within a group prior to starting therapy. However, there was a significant difference between the renal functional status of patients with mild or moderate hypertension and those with severe hypertension (Table 1A), the latter having the greatest reduction in function. Patients with severe hypertension (diastolic greater than 130 mm. Hg) also had a higher incidence of complications (Table 1B) but again there was little difference between treated and untreated patients within each group, during the control observation period. Thus the status of the treated and untreated patients in each group prior to therapy was comparable.

In Table II there is a comparison of the renal functional status during the follow-up (D₁) period as compared to the control period (C) in

treated and untreated patients of both groups I and II. There was no difference in function in treated patients in group I (mild to moderate blood pressure elevation) between the control period (C) and follow-up period (D₁), which was twenty-eight months for the group. The untreated patients in this group (group I) with mild to moderate hypertension showed a reduction in renal blood flow from 966 cc./minute to 755 cc./minute, but otherwise no significant change occurred. The mean blood pressure for the treated patients before and after treatment was 152 mm. Hg and 114 mm. Hg, respectively ($p < 0.001$). This compares to 140 mm. Hg and 141 mm. Hg in the untreated patients. The degree of blood pressure control was as follows: Of the fourteen patients in group I who were treated, the average upright diastolic pressure during the treatment period was less than 100 mm. Hg in all but two patients. In the two exceptions it was 110 and 113 mm. Hg. In the treated patients in group II (patients with severe hypertension) there was no change in renal function before and following treatment, although the mean blood pressure was reduced from 173 mm. Hg to 120 mm. Hg ($p < 0.001$) during a follow-up period of twenty-six months. (Table II.) Of the thirty-one treated patients in group II with control diastolic pressures of more than 130 mm. Hg, the upright diastolic blood pressure during therapy was less than 100 mm. Hg in fifteen patients, between 100 and 120 mm. Hg in fourteen patients and between 121 and 130 mm. Hg in two patients. There were no patients in whom the diastolic blood pressure was more than 130 mm. Hg during therapy. The untreated patients in this group showed a marked reduction in function over a follow-up period of only twenty-four months. The control blood urea nitrogen for the untreated patients was 28 mg. per cent compared to 91 mg. per cent during the follow-up period (D₁). The control glomerular filtration rate and renal blood flow in these patients were 74 cc./minute and 648 cc./minute, respectively, compared to 48 cc./minute ($p < 0.01$) and 395 cc./minute ($p < 0.01$) for these functions at the time of the follow-up observations of renal function. In addition, there was a slight rise in the mean blood pressure from 183 mm. Hg to 192 mm. Hg. (Table II.) Treated patients in both groups showed a significant improvement in electrocardiographic changes and decrease in size of the heart by x-ray.

* Hexamethonium supplied by Burroughs Wellcome & Co., Inc., Warner-Chilcott Laboratories, and Ciba Pharmaceutical Products, Inc.

† Pentolinium supplied by Wyeth Laboratories as ansolysen.®

‡ Mecamlamine supplied by Merck Sharp & Dohme as inversine.®

§ Hydralazine supplied by Ciba Pharmaceutical Products, Inc. as apresoline.®

TABLE 1A
VITAL STATISTICS AND RENAL HEMODYNAMICS PRIOR TO THERAPY

Data	Group I (diastolic pressure < 130 mm. Hg)		Group II (diastolic pressure > 130 mm. Hg)	
	Treated	Untreated	Treated	Untreated
No. of patients.....	14	8	31	11
Per cent of total.....	22	13	48	17
Average age.....	50	48	49	44
Men.....	8	4	15	9
Women.....	6	4	16	2
White.....	5	0	14	6
Negro.....	9	8	17	5
Blood pressure, supine				
Average systolic.....	212	179	226	242
Average diastolic.....	122	117	143	155
Average mean*.....	152	138	170	184
Blood pressure, upright				
Average systolic.....	209	175	224	231
Average diastolic.....	123	122	147	158
Average mean*.....	152	140	173	183
Average blood urea nitrogen (mg. %)... ..	18	16	27	28
Average glomerular filtration rate (cc./min.).....	94	98	75	74
Average renal blood flow (cc./min.).....	899	966	675	648

* Mean blood pressure (diastolic + $\frac{1}{3}$ pulse pressure).

TABLE 1B
COMPLICATIONS OF HYPERTENSION IN PATIENTS PRIOR TO THERAPY

Data	Group I (diastolic pressure < 130 mm. Hg)				Group II (diastolic pressure > 130 mm. Hg)			
	Treated		Untreated		Treated		Untreated	
	No.	%	No.	%	No.	%	No.	%
Patients.....	14	..	8	..	31	..	11	..
Abnormal urine.....	3	21	5	62	23	74	10	91
Abnormal electrocardiogram.....	8	57	4	50	26	84	10	91
Abnormal x-ray*.....	5	36	4	50	25	81	10	91
Previous infarction.....	0	0	0	0	2	6	0	0
Previous cerebrovascular accident....	3	21	1	13	5	16	2	18
Funduscopy								
Grades 1 and 2.....	11	79	6	75	13	42	2	18
Grades 3 and 4.....	3	21	1	13	18	58	9	82
Heart failure								
Class I.....	5	36	0	0	8	26	0	0
Class II.....	2	14	1	13	3	10	0	0
Class III.....	0	0	3	37	5	16	3	27
Class IV.....	0	0	0	0	1	3	0	0

* Refers to abnormalities of heart only.

TABLE II
COMPARISON OF CONTROL AND FOLLOW-UP RENAL FUNCTION IN TREATED AND UNTREATED HYPERTENSIVE PATIENTS

Data	Group I (diastolic pressure < 130 mm. Hg)				Group II (diastolic pressure > 130 mm. Hg)			
	Treated		Untreated		Treated		Untreated	
No. of patients.....	14		8		31		11	
	C	D ₁	C	D ₁	C	D ₁	C	D ₁
Blood urea nitrogen (mg. %)	18	19	16	19	27	29	28	91
Glomerular filtration rate (cc./min.)	94	87	98	86	75	72	74	48
Renal blood flow (cc./min.)	899	879	966	755	675	635	648	395
Mean blood pressure (mm. Hg)	152	114	140	141	173	120	183	192
Follow-up.....	28 mo.		29 mo.		26 mo.		24 mo.	
Improved electrocardiogram (%)	...	50	...	0	...	19	...	0
Improved x-ray (%)	...	20	...	12	...	40	...	0

NOTE: C = control function.
D₁ = Follow-up function.

TABLE III
PROGNOSIS OF HYPERTENSIVE PATIENTS BASED ON
GLOMERULAR FILTRATION RATE

Glomerular Filtration Rate (cc./min.)	No. of Patients		Mortality			
	Treated	Untreated	Treated		Untreated	
			No.	%	No.	%
>100....	19	14	2	10	5	36
80-99....	15	9	2	13	3	33
60-79....	16	12	3	19	6	50
40-59....	5	10	1	20	10	100
<40....	7	9	3	43	9	100
Total....	62	54	11	18	33	61

The prognosis of hypertensive patients based upon the glomerular filtration rate prior to therapy is shown in Table III. One-hundred and sixteen of the original 133 patients who could be followed up adequately have been divided into five groups, according to initial glomerular filtration rate. Each of these groups is divided into treated and untreated patients and the number and per cent mortality calculated for both treated and untreated patients. These results show that the mortality increases and the prognosis becomes worse as the glomerular filtration rate decreases. This is true in both

TABLE IV
CAUSES OF DEATH

Cause	Number (Total)	Treated		Untreated	
		No.	%	No.	%
Uremia.....	15	0	0	15	100
Cerebrovascular accident.....	19	9	47	10	53
Cardiac.....	4	0	0	4	100
Cerebrovascular accident with uremia.....	3	1	33	2	67
Others.....	3	1	33	2	67
Total.....	44	11	25	33	75
Average survival time (mo.).....	..	22	..	11	..
Average blood urea nitrogen (mg. %)	..	30	..	46*	..
Average glomerular filtration rate (cc./min.).....	..	68	..	56	..
Average renal blood flow (cc./min.).....	..	616	..	515	..
Average mean blood pressure (mm. Hg).....	..	169	..	170	..

* This value is high by virtue of two patients having marked elevation in the BUN: If these two patients are not included the BUN would be 36.

treated and untreated patients. However, untreated patients show a much higher mortality than treated patients in each group. The mortality in untreated patients with a glomerular filtration rate below 60 cc./minute was 100 per cent. Overall, the mortality for treated patients in this series was 18 per cent compared to 61 per cent in untreated patients.

Table IV lists the causes of death in the forty-four patients who have died. In all except three cases the cause of death was directly related to the hypertension. The number and per cent of

patients dying from each cause are listed separately for both treated and untreated patients. The control renal functional status and average survival time for each group are also presented. (By survival time is meant the duration in months from the time the patient was first seen

TABLE V
COMPARISON OF FOLLOW-UP RENAL STATUS IN TWENTY-ONE
TREATED AND UNTREATED PATIENTS WITH
MALIGNANT HYPERTENSION

Data	Treated		Untreated	
	No.	%	No.	%
Patients.....	12	57	9	43
Mortality.....	2	17	9	100
Survival time or follow-up period if living.....	29 mo.	...	12 mo.	...
Average.....	C	D ₁	C	D ₁
Blood urea nitrogen (mg. %)... ..	31	27	29	106
Glomerular filtration rate (cc./min.)... ..	66	68	70	44
Renal blood flow (cc./min.)... ..	513	579	628	351
Mean blood pressure (mm. Hg.)... ..	175	122	184	197
Duration (C - D ₁)... ..	28 mo.	...	10 mo.	...
Improved (%).....
Urinalysis.....	36	...	0	...
Electrocardiogram.....	54	...	0	...
X-ray.....	54	...	0	...

in the clinic to the time of his death and excludes any preceding history of hypertension.)

The control renal functional status of the two groups prior to treatment are comparable if the markedly elevated blood urea nitrogen in two of the untreated patients is excluded from the average. The mean blood pressures for the two groups are also comparable. Fifteen patients died in uremia; all of these were untreated. Nineteen patients died from cerebral vascular accidents. Nine of these were treated and ten were untreated. It should be pointed out that five of the nine treated patients who died from cerebral vascular accidents voluntarily stopped taking their medications shortly before dying. The blood pressure was adequately controlled in all five of these patients at the time that they discontinued therapy. The average survival time for these five patients after discontinuing treatment was three months, suggesting a "rebound" rise in the blood pressure resulting in death from a cerebral vascular accident. Four patients died from cardiac complications (two in congestive heart failure and two from myocardial infarction). All four patients were in the untreated group. Death in three patients could have been attributable to either a cerebral vascular accident or uremia, since both were

present. One of these patients was treated and two were untreated. Three patients died from causes not related to their hypertension. Of these, one died from pneumonia, one from carcinoma of the breast, and one from a dissecting aneurysm. The data demonstrate clearly that

TABLE VI
FOLLOW-UP IN THIRTY-ONE PATIENTS WITH
MALIGNANT HYPERTENSION

Cause of Death	Treated Patients*	Untreated Patients†
No. of patients observed.....	13	18
Cerebrovascular accident.....	1	3
Cerebrovascular accident + uremia.....	1	1
Uremia.....	0	11
Cardiac.....	0	2
Average survival time (mo.) or follow-up period if living..	30	14

* Thirteen patients treated, eleven living, two dead.

† Eighteen patients untreated, one living, seventeen dead.

there was a much higher incidence of death in untreated patients. Of the patients who died, 75 per cent were untreated. The average survival time in treated patients who died was twenty-two months, compared to eleven months in those who were not treated.

In Table v twenty-one patients with malignant hypertension with control (C) and follow-up (D₁) renal function studies are compared. These patients were analyzed separately only to point out the rapid progression of this disease. Of the twenty-one patients, twelve patients were treated and nine were untreated. Only two of the twelve treated patients have died to date and the average follow-up period for the entire group of twelve is now twenty-nine months. All nine of the untreated patients have died and the average survival time was twelve months. The renal functional status of the twelve treated patients did not change over a follow-up period averaging twenty-eight months, although the mean blood pressure was effectively reduced from 175 mm. Hg to 122 mm. Hg. In contrast to this, the renal function of the nine untreated patients was reduced to approximately 60 per cent of control values ($p < 0.01$) following a period of only ten months. The mean blood pressure in

TABLE VII

OBSERVATIONS ON CONTRALATERAL KIDNEY IN PATIENTS WITH UNILATERAL RENAL ARTERY OCCLUSION*

Case No.	Collateral Therapy	Therapy for Hypertension	Glomerular Filtration (cc./min.)			Renal Blood Flow (cc./min.)			Blood Urea Nitrogen (mg. %)			Upright Blood Pressure†						Time Interval‡		Result
												Systolic			Diastolic			Months		
			C	D ₁	D ₂	C	D ₁	D ₂	C	D ₁	D ₂	C	D ₁	D ₂	C	D ₁	D ₂	D ₁	D ₂	
I	Aortic homograph	Nephrectomy	36	54	62	195	480	666	48	28	16	270	180	132	192	110	90	6	26	Died, ruptured homograph
II	None	Nephrectomy	55	60	80	744	800	940	18	24	18	244	176	160	156	118	96	10	18	Living and well
III	None	Nephrectomy, rauwolfia plus pentolinium	20	35	54	110	200	480	82	64	36	210	180	160	168	120	90	3	36	Living and well
IV	None	Rauwolfia plus pentolinium	46	54	58	420	510	440	32	30	28	196	154	130	142	110	100	4	19	Died after 2 years, coronary occlusion
V	Aortic homograph	Rauwolfia plus mecamlamine	25	60	56	130	725	650	70	30	36	230	160	150	160	110	92	6	24	Living and well

* The ureter to the occluded kidney was catheterized in each patient but there was no urine formation and consequently renal function could not be measured.

† Retinal hemorrhages and papilledema were present in all five patients.

‡ Period of time between control observation and follow-up observation on renal function.

C = Control.

D₁ = First observation after therapy was instituted.

D₂ = Final observation after therapy was instituted.

this group increased from 184 mm. Hg to 197 mm. Hg, and the blood urea nitrogen from an average value of 29 mg. per cent to 106 mg. per cent. There was improvement in the urinary findings, electrocardiograms and size of the heart in treated patients, ranging from 36 per cent to 54 per cent of those who had abnormal findings initially. None of the patients in the untreated group showed improvement in these abnormal findings. Table VI summarizes the clinical status and results of therapy in thirty-one patients with malignant hypertension. This includes the twenty-one patients in Table V in whom follow-up differential renal function studies were obtained.

In Table VII are summarized the observations made on five patients with unilateral renal artery occlusion due to thrombosis resulting from severe atherosclerosis. Each of these patients had moderately severe to severe hypertension at the time of the study. In each case the onset of severe hypertension was rather acute, apparently occurring soon after the renal artery was occluded by thrombosis. All patients had malignant hypertensive retinopathy as indicated by papilledema and retinal hemorrhages. Differential renal function studies showed moderate to marked depression in renal function* in three

patients, indicating minimal to severe renal damage in the unoccluded kidney. This apparently resulted from the elevated blood pressure to which the unoccluded kidney was exposed. In two patients, renal function in the unoccluded kidney was depressed to less than 50 per cent of normal for one kidney and in the third it was about two-thirds of the normal value. As therapy was instituted and the blood pressure was reduced, renal function improved progressively in the unoccluded kidney. This occurred whether the blood pressure decreased as a result of drug therapy or as a result of removal of the kidney with the occluded renal artery. The most dramatic improvement in renal function occurred in the two patients (Case III and V) who showed the most severe depression prior to antihypertensive therapy. The blood pressure was maintained at normotensive levels following nephrectomy in two patients. Nephrectomy was also performed in a third patient but the blood pressure did not decrease and medical therapy (pentolinium plus rauwolfia) was necessary to control the blood pressure. The fourth patient refused surgery and was treated medically with ganglionic blockade (mecamylamine plus rauwolfia). The fifth patient is presented in detail.

CASE I. A forty-six year old patient had marked atherosclerosis of the aorta, which involved the right renal artery and was followed by formation of

* Normal glomerular filtration rate for one kidney is in excess of 55 cc./minute.

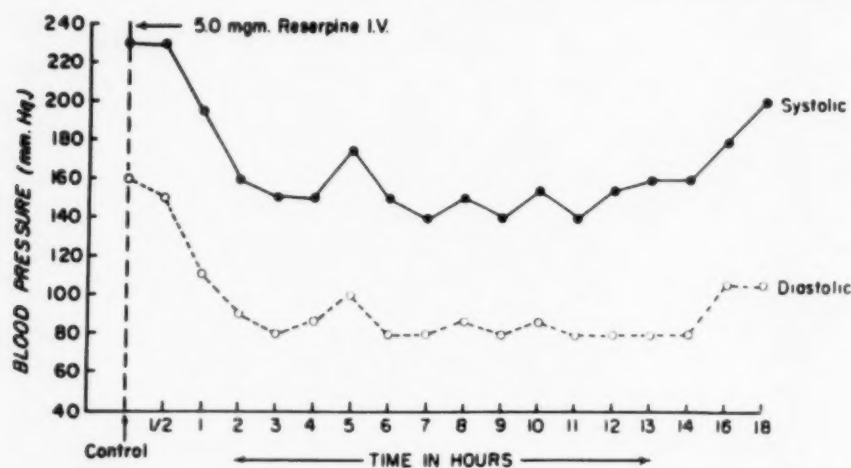


FIG. 2A. (Patient G. L. M.). The acute blood pressure response to reserpine (a centrally acting sympathetic depressant agent) in a patient with malignant hypertension of renal origin (arterial occlusion of one renal artery). The blood pressure was continued at this reduced level for a period of two weeks following which the patient was given alseroxylon and mecamlamine.

	Glomerular Filtration Rate ml/min.		Renal Blood Flow ml/min.	
	Right (occluded)	Left	Right (occluded)	Left
Control	0	25	0	130
Blood Pressure Rx.	0	35	0	200
Homograph				
1 month	0	45	0	425
6 month	0	60	0	725

FIG. 2B. There was progressive improvement in renal function in the unoccluded kidney following blood pressure reduction.

a thrombus which completely occluded the right renal artery. The left renal artery was not involved. When admitted to the hospital the patient had marked encephalopathy, retinal hemorrhages (Fig. 3A), papilledema and convulsions as a result of malignant hypertension, probably secondary to the ischemic kidney (Goldblatt kidney). He was given parenteral reserpine in a dose of 5 mg. every six hours. (Fig. 2.) This reduced the blood pressure effectively, following which most of the cerebral manifestations subsided. Therapy was changed gradually to a combination of oral rauwolfia and a ganglionic blocking agent, mecamlamine (inversine®). After blood pressure control was achieved, a homograph replacement of the aorta was performed. His blood pressure has since been well regulated for a period of two years and he is in full-time employment. His blood pressure and renal functional response to therapy are summarized in Figure 2B. It is obvious that no return of renal function was achieved in the occluded kidney (right). However, in the opposite kidney (left), glomerular filtration rate and renal blood flow, which were depressed to less than 50 per cent of normal for one kidney prior to therapy, increased gradually so that now they are

approximately normal. His blood urea nitrogen decreased from 70 to 30 mg. per 100 cc.

Undoubtedly, the depression in function in the unoccluded kidney in this patient was due to acute vascular damage (severe vasoconstriction and intrarenal hemorrhages) rather than to chronic deterioration which decreased the functional capacity of this kidney. Since the process was relatively acute, it was reversible. Had the hypertension and increased sympathetic vasoconstrictor response been permitted to persist, progressive renal failure would probably have developed, provided the patient did not first die of cerebral manifestations. Furthermore, if the initial depression in renal function had been due to chronic deterioration of the kidney, the marked improvement in function which followed therapy would probably not have occurred. This was the case in the right kidney. Despite the fact that circulation was re-established following aortic homograph re-

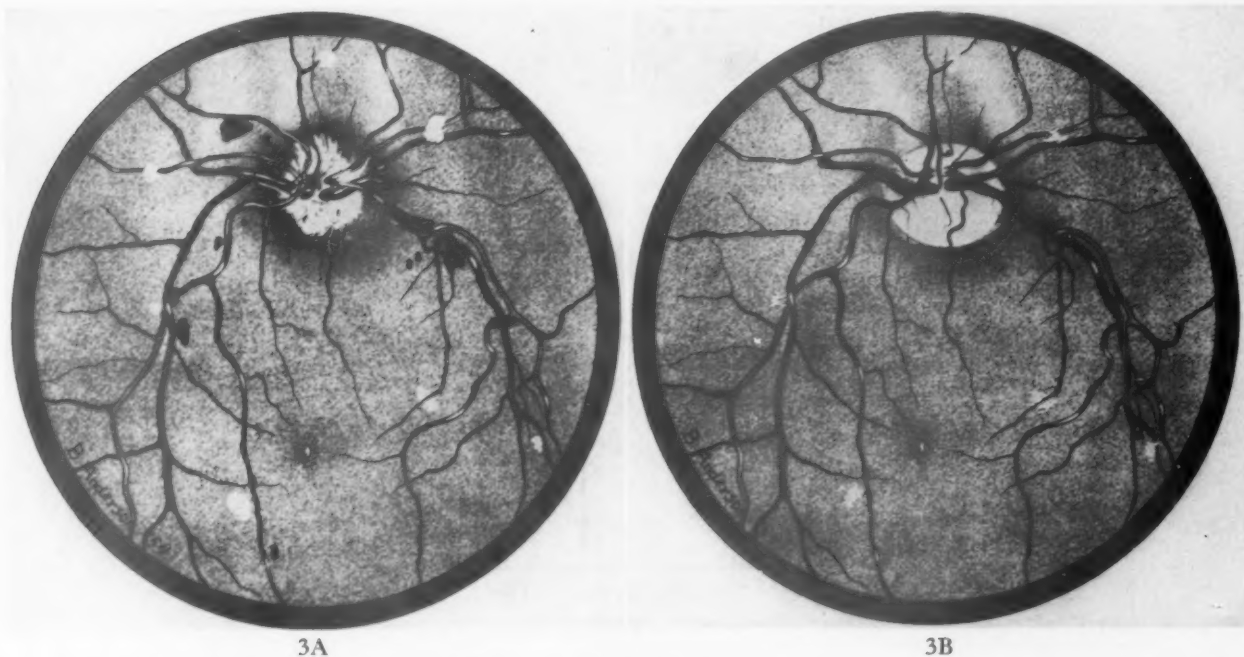


FIG. 3. A, funduscopy changes in patient G. L. M. prior to antihypertensive therapy. B, funduscopy changes following antihypertensive therapy for a period of one month.

placement, there was no return of function in this kidney. This case is a typical clinical counterpart of the "ischemic kidney" that has been produced in dogs. Therefore, we can conclude that even in the patient with primary renal disease and hypertension secondary thereto, benefit can be derived from effective antihypertensive therapy.

COMMENTS

The results clearly demonstrate the value of effective treatment of hypertension in arresting renal vascular deterioration associated with this disease. This fact is brought out by the follow-up renal functional status of the untreated patients in group II. These patients had severe hypertension as judged by the control diastolic blood pressure elevation and, when untreated, showed a decline in glomerular filtration rate (Fig. 4A) and renal blood flow (Fig. 4B) to approximately two-thirds of the control value. This was associated with a rising blood pressure and blood urea nitrogen. Patient R. L. (Fig. 5) is a typical example. In contrast, the treated patients in group II (Figs. 4A and 4B) had a very satisfactory decrease in blood pressure and showed no deterioration in renal function status (Fig. 6, patient W. S.). It should be emphasized that there was usually no improvement in renal functional status in this group, only arrest of the

vascular deterioration observed in those who were treated. Similar observations have been made by Perry and Schroeder [18]. As a matter of fact, one might anticipate that no significant improvement in function would be expected to occur in patients with slowly progressing renal damage since the injured nephrons are slowly replaced by scar tissue. However, in patients experiencing renal damage due to severe hypertension of relatively acute onset, some improvement in renal function was sometimes observed when the blood pressure was reduced effectively and without delay (Fig. 7, patient A. M.).

In patients with mild hypertension there was no difference in vascular deterioration in the treated and untreated patients, such as was observed in the severe cases, probably due to the slower rate of renal deterioration in such patients, which requires a longer period of time for demonstration than our follow-up period of two to five years. The fact that there was no significant difference in renal functional status between treated and untreated patients with mild to moderate hypertension (other than mild depression in the renal blood flow) might lead some to question the efficacy of treatment in this type of patient. There are, however, several good reasons for active, early treatment of hypertension in this type of patient. In the first place, the transition from normal to abnormal renal func-

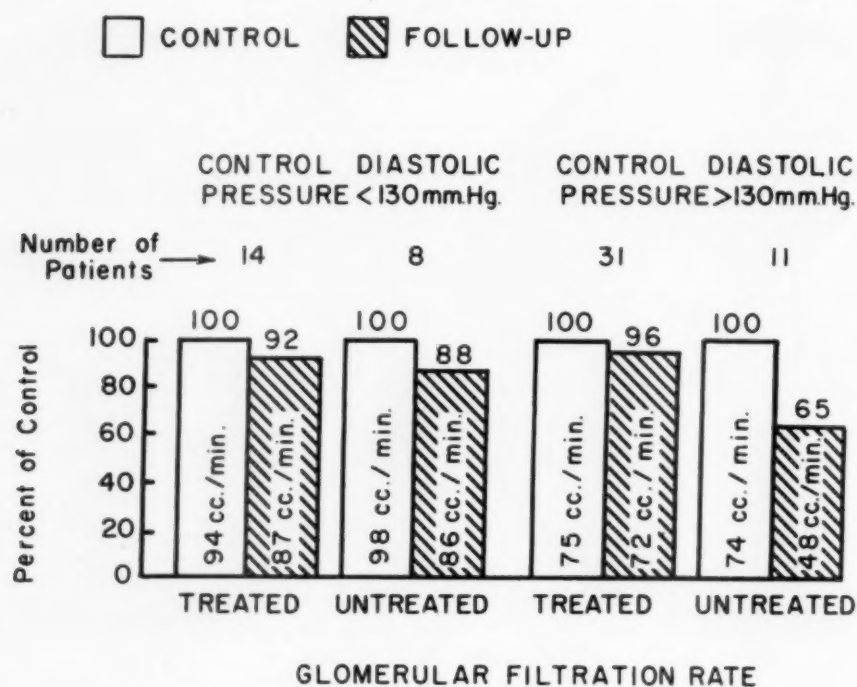


FIG. 4A. Summary of observations on glomerular filtration rate in treated and untreated patients with hypertension.

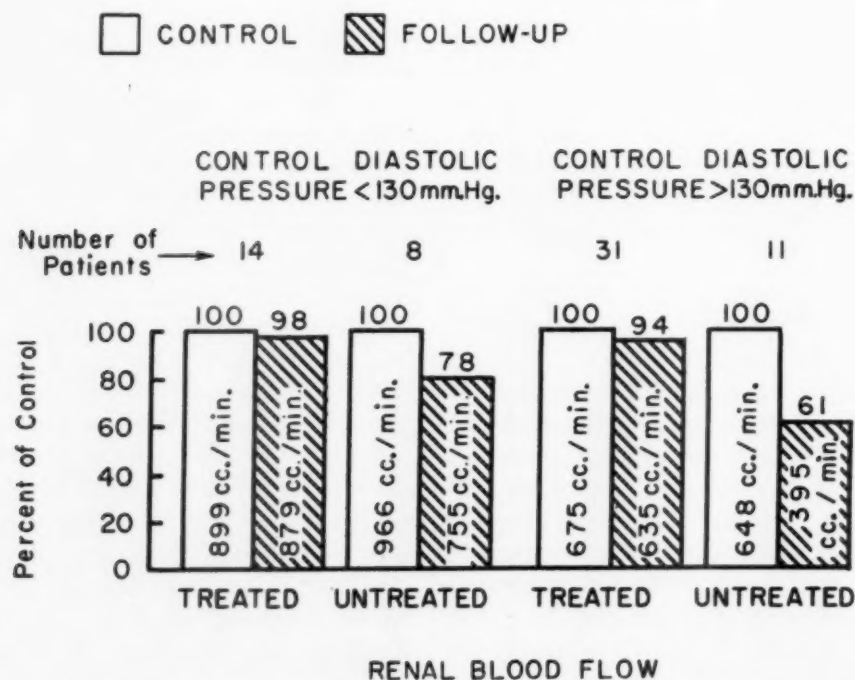


FIG. 4B. Summary of observations on renal blood flow in treated and untreated patients with hypertension.

tion does occur somewhere in the course of the disease in patients with hypertension of this severity [7], since neither the treated nor the untreated patients in group 1 had normal clearance values at the time the control observations were made, indicating that some renal

deterioration had already occurred. In our present state of knowledge we cannot say at what point the transition occurs. The evidence suggests, however, that the higher the blood pressure, the greater the degree of renal damage. Since it has been demonstrated that deteriora-

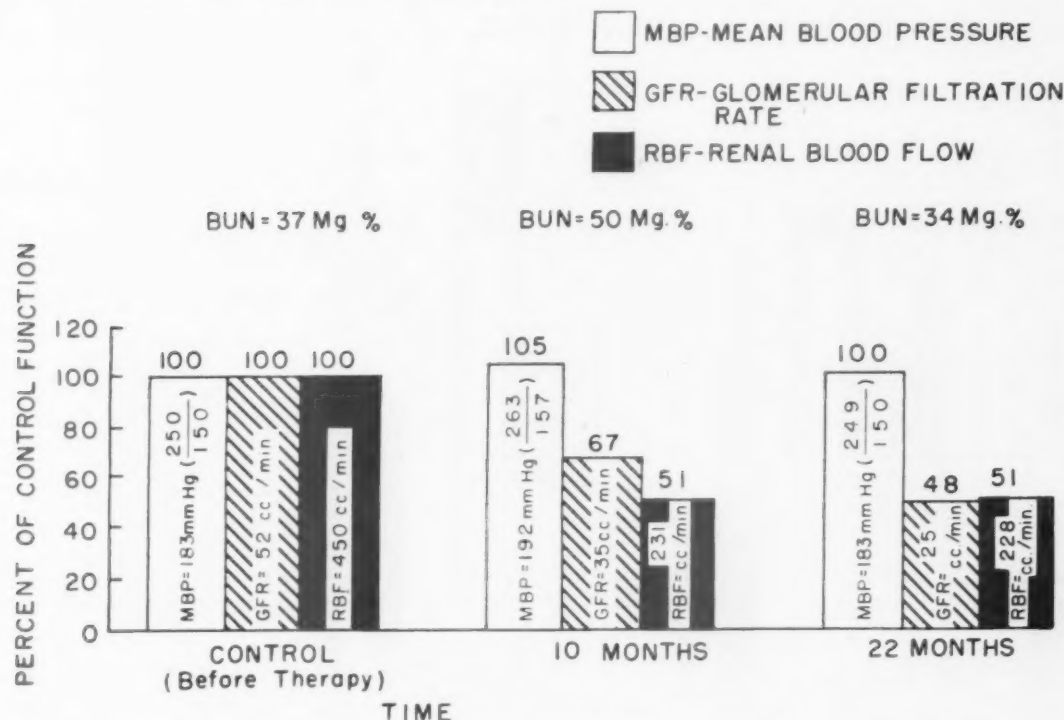


FIG. 5. (Patient R. L.). The effect of severe (non-malignant) hypertension on renal function over a period of two years in a patient who was not treated with antihypertensive therapy.

tion of renal function can be arrested by treatment in severe cases, it seems only reasonable to suppose that early treatment of the mild and moderately severe case would be of even greater value in delaying or preventing the vascular deterioration in the kidney. That this deterioration was a slow process in patients with mild and moderate hypertension is borne out by the lack of difference in control and follow-up observations of renal clearances in treated and untreated patients. The slow nature of the disease process in these patients can be used to advantage by the clinician, for it is in this type of patient that the blood pressure can be reduced gradually and much more effectively over a longer period of time, thereby preventing some of the untoward reactions to rapid reduction of the blood pressure. Finally, there is evidence to indicate that improvement occurs in the electrocardiogram, associated with a decrease in heart size of the treated patients, not only in those with severe hypertension but in patients with mild type hypertension as well.

An additional reason for active and early treatment of patients with hypertension is presented in Table III. As the glomerular filtration rate decreased, a reflection of vascular deterioration, there was an increase in mortality in both treated and untreated patients. The

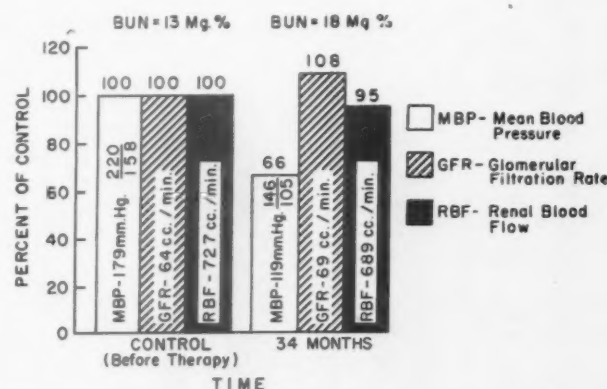


FIG. 6. (Patient W. S.). Renal effects of severe hypertension (non-malignant) on renal function in a patient who was treated for a period of three years with antihypertensive therapy. Note that there was no further deterioration of the renal vascular system, as indicated by the glomerular filtration rate and renal blood flow following institution of antihypertensive therapy. Compare this response with Figure 5 (Case R. L., untreated) showing evidence of progressive vascular deterioration over a period of two years.

mortality rate in untreated patients (the total number of patients followed up) was three times that of the treated patients. The results in Table II indicate that treatment, by arresting renal deterioration, will keep a patient from falling into a group with a lower renal function and hence a worse prognosis. Secondly, once a

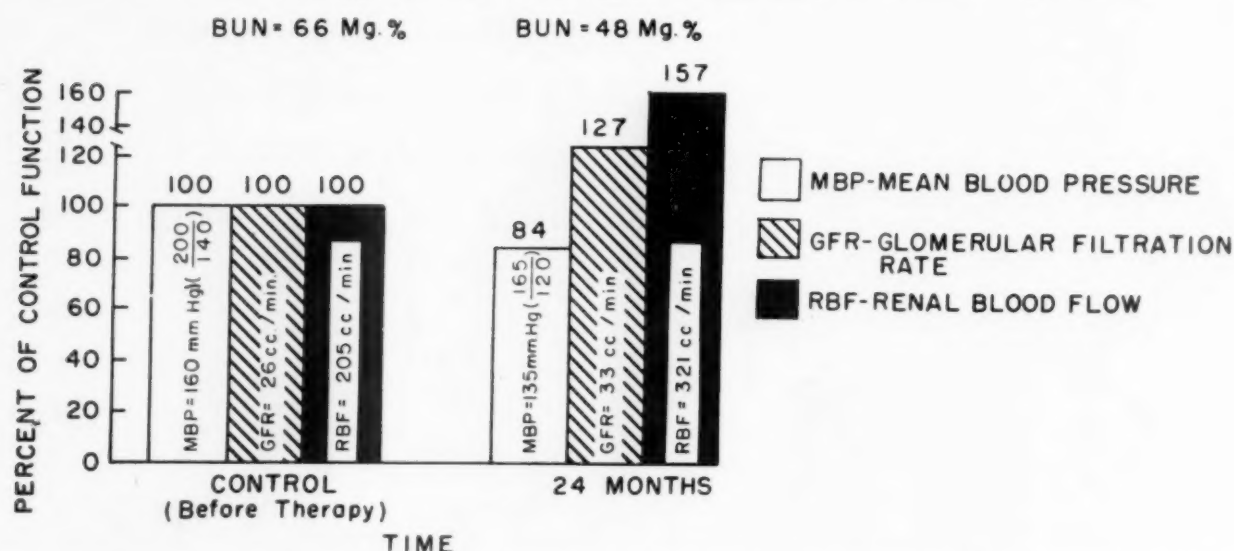


FIG. 7. (Patient A. M.). Effect of severe hypertension (non-malignant) on renal function. This patient showed a slight increase in glomerular filtration rate and renal blood flow following antihypertensive therapy for a period of two years.

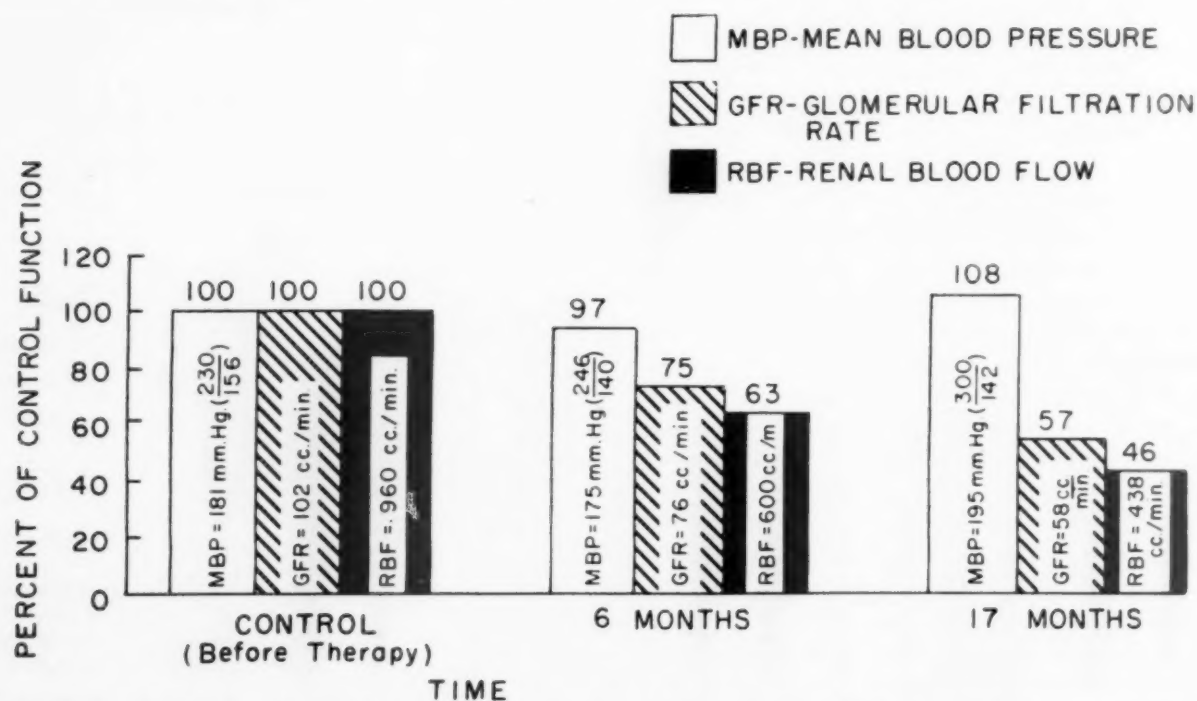


FIG. 8. (Patient J. E.). A patient with malignant hypertension who was not treated for a period of seventeen months. There was progressive reduction in glomerular filtration rate and renal blood flow. A few weeks after the last renal function test was performed the patient died of congestive heart failure and renal failure.

patient is in a lower function group his prognosis is better with than without treatment. (Table III.)

Further evidence for effective treatment is presented in Table II. Seventy-five per cent of the patients who died were untreated. None of the patients who were treated died of uremia as the sole cause of death. This is in contrast to fifteen untreated patients who died in uremia. Five of

the nine treated patients who died as a result of cerebral vascular accidents had had effective treatment and control of their blood pressure, but then voluntarily discontinued treatment. All five were dead in less than a three-month period after discontinuation of their medication. Unfortunately, we have blood pressure observations on only three of these patients after they discontinued treatment; in all three a sudden

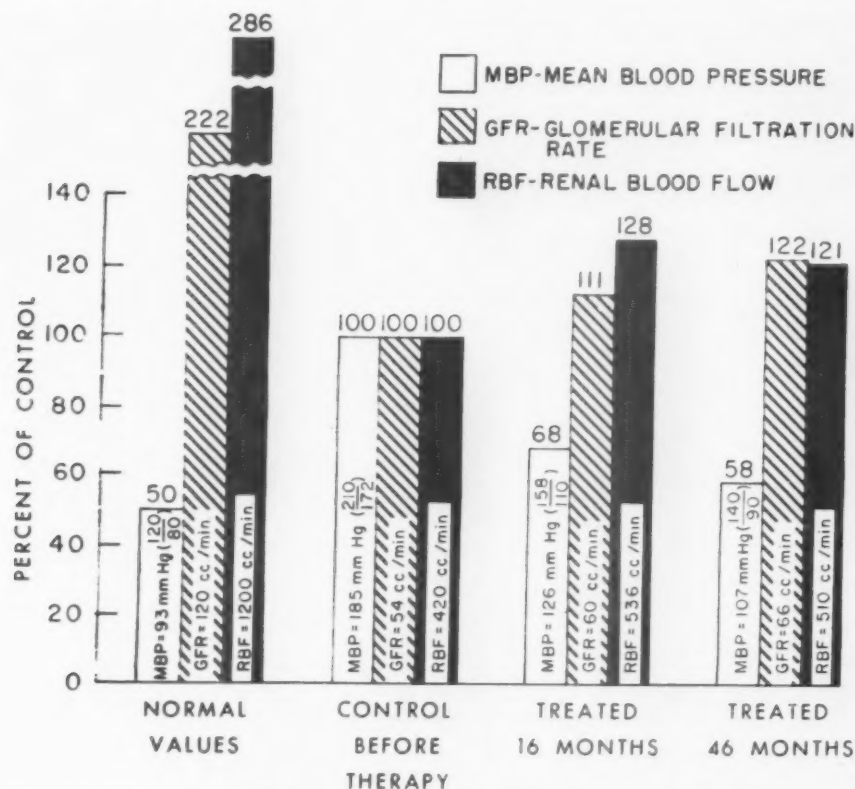


FIG. 9A. (Patient T. H.). Summary of results in a patient with malignant hypertension who was treated effectively with antihypertensive agents (rauwolfia plus ganglionic blockade). Prior to the institution of therapy the glomerular filtration rate and renal blood flow were depressed to less than 50 per cent of normal due to the vascular deterioration associated with malignant hypertension. However, following effective antihypertensive therapy for a period of four years there was no further reduction in glomerular filtration rate and renal blood flow. This indicates that the vascular deterioration associated with malignant hypertension can be arrested by effective antihypertensive therapy.

rise in blood pressure occurred shortly thereafter, and this presumably resulted in hemorrhage into the brain. The same sequence of events probably occurred in the other two patients. These patients emphasize not only the value of antihypertensive treatment but also the importance of maintaining treatment once it has been started. Sudden withdrawal of drugs is as disastrous as no treatment at all.

The value of treatment is clearly shown in twenty-one patients with malignant hypertension who had follow-up renal studies. In the treated patients, the renal deterioration was arrested in association with a significant reduction in mean blood pressure from 175 to 122 mm. Hg for the group, over a follow-up period of twenty-eight months. This is in contrast to the decrease in function in untreated patients (Table v). Patient J. E. (Fig. 8) is a typical patient with malignant hypertension who was not treated. The progressive renal vascular

deterioration is evident. By contrast, patient T. H. (Fig. 9A) was treated and the renal vascular deterioration was arrested.

Malignant hypertension is almost uniformly rapidly fatal if not treated. Thirty-two of the original 133 patients had malignant hypertension. We were able to follow thirty-one of the thirty-two patients. Thirteen of the patients had been treated and of these only two are dead. Seventeen of eighteen untreated patients are now dead, eleven of whom died in uremia. The average follow-up period for the treated patients is now thirty months and the average survival time for the untreated patients was fourteen months. The one untreated patient with malignant hypertension who is still living refuses therapy and has been followed up for fifteen months.

In Figures 5 through 9 case reports are presented to demonstrate graphically the typical effect of hypertension in treated and untreated patients. The patient represented in Figure 5

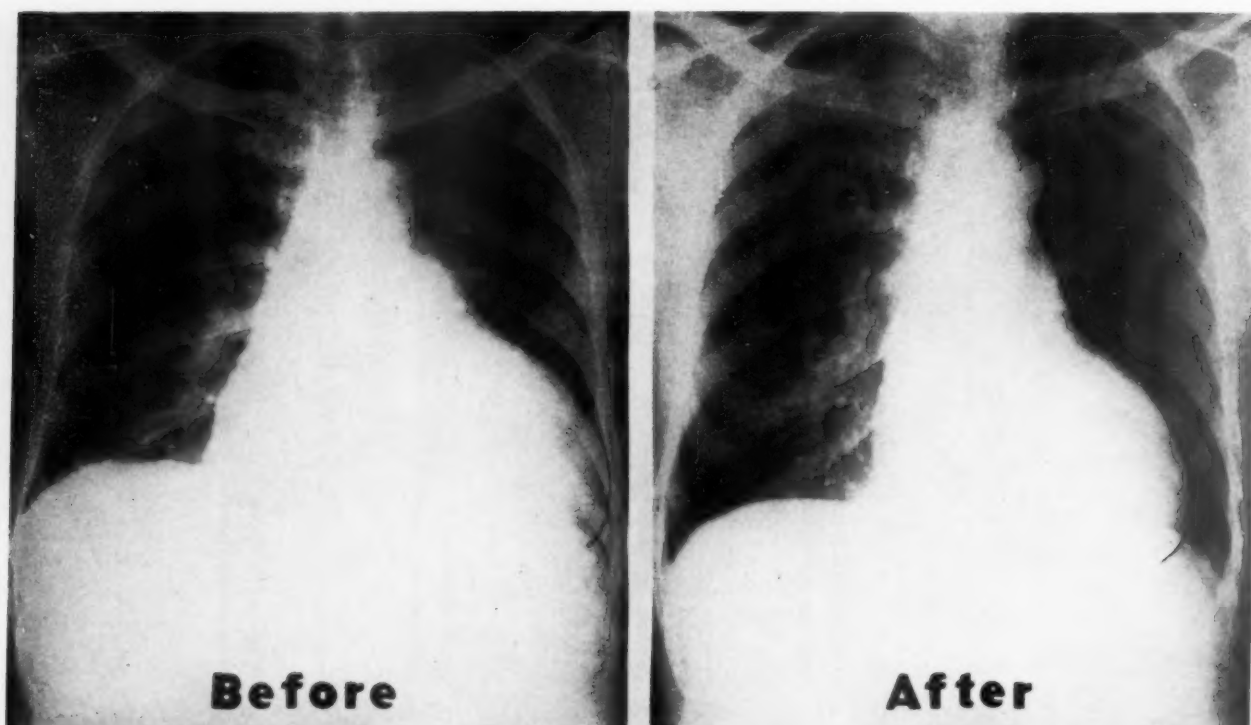


FIG. 9B. Associated with the reduction in blood pressure in this patient with malignant hypertension, there was a definite decrease in the size of the heart. This occurred with no therapy other than blood pressure reduction.

was a fifty-three year old Negro man who when first seen in the clinic had an average upright control blood pressure of 250/150 mm. Hg. His control renal clearances were less than half of normal. No effective drugs were available at the time so this patient remained untreated. Ten months later his function was further reduced to about 60 per cent of his control values (one-fourth to one-third of normal) and his pressure remained elevated. Twenty-two months after his initial function studies the glomerular filtration rate had decreased still further. This patient ultimately died from a cerebral vascular accident.

The case report summarized in Figure 6 represents a patient with hypertension of severity equal to the patient in Figure 5. His function was approximately two-thirds of normal. He was started on treatment and has had satisfactory control since then. His renal functional status thirty-four months later has not changed and his blood pressure has been reduced to almost normotensive levels. Most of his symptoms have disappeared and there has been improvement in the electrocardiogram and decrease in size of the heart by x-ray examination.

The patient in Figure 7 was a person with severe hypertension of acute onset. A significant

reduction in blood pressure was obtained with therapy. Renal function studies conducted two years after the initiation of therapy indicated a slight improvement.

The patient presented in Figure 8, who suffered from malignant hypertension, was a thirty-eight year old white man with a control blood pressure of 230/156 mm. Hg. His control renal clearances were only slightly below normal. He received no treatment; six months later his renal function was approximately 70 per cent of control values and his blood pressure remained elevated. Seventeen months after his control observations his blood pressure was still elevated and his renal function had dropped to around 50 per cent of control values. This patient died a few weeks later in congestive heart failure.

The patient in Figure 9 also suffered from malignant hypertension. When first seen in the clinic he had a pressure of 210/172 mm. Hg and his renal function was about 50 per cent of normal. He was given antihypertensive therapy and experienced a fall in blood pressure in sixteen months to 158/110 mm. Hg. His renal function at that time was slightly better than during the control observations, but had not changed significantly. Forty-six months after

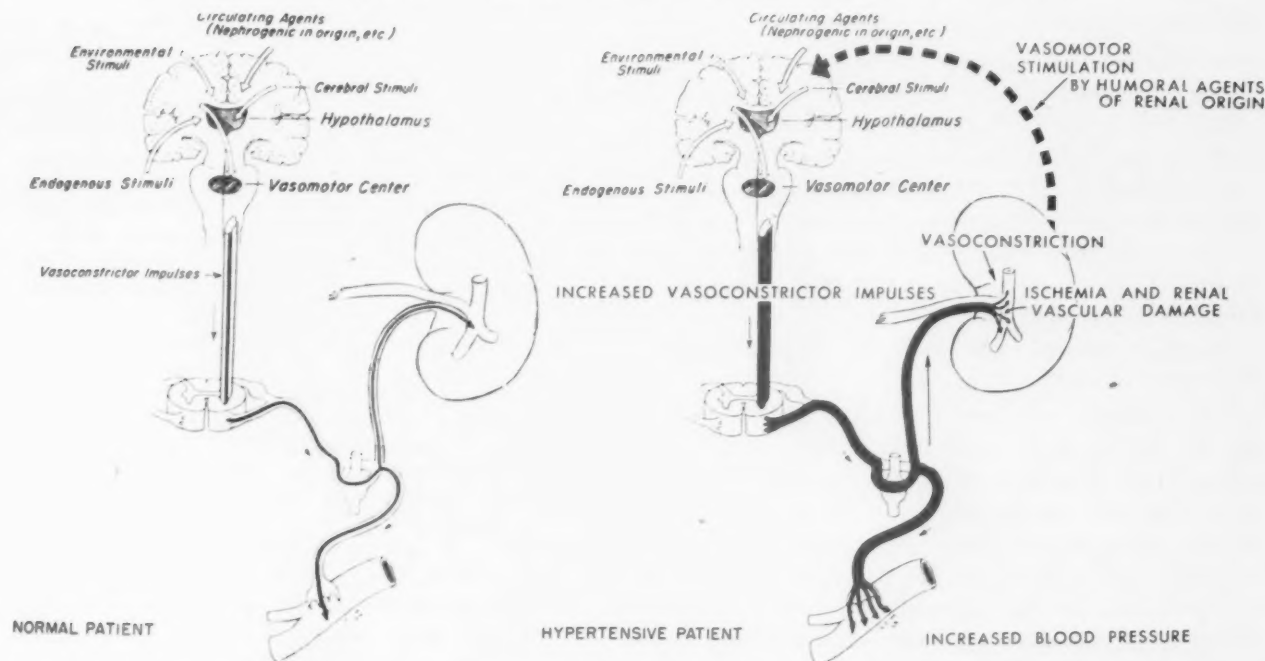


FIG. 10. Diagrammatic representation of the inter-relationship between blood pressure elevation and renal vascular deterioration. Apparently, primary renal disease can release humoral agents which stimulate the brain and consequently the sympathetic nervous system, resulting in a marked increase in blood pressure. The increase in blood pressure produces generalized vascular deterioration when it becomes sufficiently marked. This produces further renal damage which may stimulate the sympathetic nervous system and set up the vicious cycle of the malignant hypertensive syndrome. Contrariwise, hypertension of unknown origin can become sufficiently severe to produce renal vascular damage with secondary changes in the kidney. The renal vascular deterioration associated with this type of hypertension supposedly could also release humoral agents which would stimulate the sympathetic nervous system in the brain and thus produce the vicious cycle of malignant hypertension.

treatment began the blood pressure had been reduced to normotensive levels (140/90 mm. Hg) and his renal functional status remained stable. This patient is still alive and gainfully employed.

The patients with unilateral renal arterial occlusive disease demonstrate clearly that renal disease can produce hypertension and that the hypertension can in turn produce renal damage. Good evidence for the renal origin of hypertension was presented by the first two patients (Table VII) who became normotensive following nephrectomy. The glomerular filtration rate and renal blood flow were moderately depressed in the unoccluded kidney in patient No. 1, apparently as a result of the hypertensive process. When the blood pressure returned to normal, renal function in the unoccluded kidney improved dramatically, returning to normal. Similar observations were made in three additional patients, two of whom (Cases IV and V) were treated with medical therapy only. Nephrectomy was performed in the third patient but the blood pressure remained elevated. Medical antihypertensive therapy was required,

following which the blood pressure was reduced and renal function improved. The observations on these five patients support the concept that severe hypertension alone can produce generalized vascular damage, frequently most marked in the kidneys since vascular deterioration was observed in the contralateral kidney in which the blood supply was not altered but the arterial blood pressure was elevated. Furthermore, the vascular degenerative changes were not only arrested by reducing the blood pressure but blood pressure reduction by any means was accompanied by an improvement in renal function.

SUMMARY

Renal clearance studies were performed in 133 patients with hypertensive vascular disease, 116 of whom were followed for a period of two to five years. In sixty-four of these patients serial renal function studies were performed. Forty-five of the sixty-four were treated and nineteen were untreated.

Comparison of treated and untreated patients showed that effective reduction of the blood

pressure arrested the renal vascular deterioration associated with hypertension in patients with severe and moderately severe hypertension. Untreated patients with mild and moderately severe hypertension did not show the rapid renal deterioration that occurs in patients with more marked elevation of the blood pressure.

The mortality was significantly lower in treated patients than in untreated patients. Renal deterioration was arrested and mortality reduced in patients with malignant hypertension who were treated.

Five patients with hypertension due to unilateral renal artery occlusion were studied. Glomerular filtration rate and renal blood flow were reduced significantly in the contralateral kidney as a result of the severe hypertension exhibited by these patients. This vascular deterioration in the unoccluded kidney could be arrested and was partly reversible when the blood pressure was reduced effectively.

These results indicate that renal deterioration can be arrested by effective treatment of hypertension and that the lives of hypertensive patients can thus be prolonged. It is recommended therefore that hypertensive vascular disease be treated vigorously and early in the hope of decreasing the morbidity and mortality which too commonly result from this disease.

Acknowledgment: The authors wish to express their appreciation to the numerous physicians who aided in the care of these patients over the past six years. Those who assisted most actively were Drs. Edward Dennis, Warren Hughes, Lewis Mills, Robert McConn, Robert Hershberger, Sam Miller and Coleman Caplovitz.

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The Paradox of Right Ventricular Enlargement in Mitral Insufficiency*

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THE left side of the heart bears the pathophysiologic burden accruing from free mitral insufficiency. The atrial volume load is exaggerated by the quantity of blood which enters through the defective valve; that of the ventricle is increased because a larger stroke volume is required to compensate for the blood lost to the atrium. Both of these chambers tend to dilate in response to their unusual tasks.

Clinical experience supports this concept through the common association of the roentgenologic and electrocardiographic manifestations of left ventricular enlargement with major mitral insufficiency when the lesion occurs alone or in combination with minimal mitral stenosis [1,4]. Viewed differently, right ventricular enlargement accompanying mitral insufficiency suggests the presence of an additional defect as the cause of the abnormality of the right side of the heart.

The present report has resulted from a pursuit into the reliability of this generalization. It indicates that, contrary to expectation, isolated mitral insufficiency of significant degree can produce the roentgenologic and electrocardiographic evidence of right ventricular enlargement. The data for this conclusion have been derived from four patients who were subjected to cardiac catheterization and to surgical exploration of the mitral valve. It is fortified by the findings at autopsy examination of two of these patients. The explanation for the apparent paradox is based on further considerations of the abnormal physiology of mitral insufficiency, particularly in its relation to the vascular system of the lungs.

MATERIAL

The four patients, three of whom were female, had chronic rheumatic heart disease. Their ages ranged from twenty to forty years.

The diagnosis of mitral regurgitation was established by direct exploration of the valve at surgery (three cases) or necropsy (one case). The lesion was considered significant when the orifice permitted the passage of at least one and a half fingers—a calculated area greater than 3.5 sq. cm. Mitral regurgitation was also considered dynamic when the systolic jet acknowledged by the surgeon at the time of operation was estimated at greater than 2 plus (range varies from 1 to 4 plus).

METHODS

The electrocardiographic diagnoses of left ventricular hypertrophy, right ventricular hypertrophy and incomplete right bundle branch block were made according to standard criteria defined by Sokolow and Lyon [5,6] and by Barker and Valencia [7].

Cardiac enlargement was estimated in terms of 1 to 4 plus (slight to massive). Roentgenograms were taken in the usual projections at a distance of 6 feet. Left atrial enlargement was appraised by fluoroscopy and roentgenographic study according to the standard methods [8].

Right heart catheterization was carried out employing the technic of Cournand and Ranges [9]. The patients were in a fasting state with no evidence of congestive heart failure. The cardiac output was measured by the direct Fick principle while the pulmonary venous capillary pressure was determined according to the method of Hellems and co-workers [10]. Phasic and mean pressures were recorded on a direct-writing oscillograph. Mean pressures were obtained by electrical integration at the time of recording. The zero point for all pressures was taken at 10 cm. anterior to the spine with the patient in the

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recumbent position. Mean pulmonary artery pressure was recorded with the tip of the catheter in the main stem of the pulmonary artery.

Resistances were calculated according to the Poiseuille equation in which resistance equals pressure gradient.

Pulmonary arteriolar resistance was rate of blood flow then calculated according to the formula: $R = \frac{P_{Am} - "PVC"}{CO} \times 1332$ dynes/second. cm^{-5} , and

total pulmonary resistance as follows: $R' = \frac{P_{Am}}{CO} \times 1332$ dynes/second/ cm^{-5} in which P_{Am} = pulmonary arterial mean pressure in mm. Hg, "PVC" = pulmonary venous capillary pressure in mm. Hg, CO = cardiac output in cc. per second, 1332 = conversion factor from mm. Hg to dynes per cm^2 .

Postmortem examination was carried out in two patients. The technic of Edwards [6] was employed in the analysis of the pulmonary vascular changes. Microscopic preparations of the lung tissue were stained with hematoxylin and eosin. Verhoeff's elastic tissue stain counterstained with Van Gieson's connective tissue stain was also used.

CLINICAL DATA (TABLE 1)

Two patients gave a history of rheumatic fever. Eventually all demonstrated the manifestations of right heart failure. In three, these were the first indications of cardiac decompensation; in the remainder they succeeded mild episodes of exertional dyspnea.

Atrial fibrillation and the characteristic pattern of right ventricular hypertrophy was noted on the electrocardiogram in each. (Figs. 1 and 2.) Cardiac roentgenograms demonstrated significant enlargement of the pulmonary artery segment, the right ventricle and the left atrium. (Fig. 3A.) The degree of ventricular dilatation and hypertrophy was often difficult to assess although the right ventricle appeared to be more prominent in size than the left.

CARDIAC CATHETERIZATION (TABLE 1)

All four patients showed a marked reduction in cardiac output, ranging from 2.1 to 2.8 L./

TABLE 1
CLINICAL, ELECTROCARDIOGRAPHIC, ROENTGENOGRAPHIC, RIGHT HEART CATHETERIZATION AND SURGICAL DATA

Case	Duration of Left Ventricular Failure	Duration of Right Ventricular Failure	Rhythm	Electrocardiogram	Left Atrial Enlargement*	Right Heart Catheterization								Mitral Valve Orifice Area (cm. ²)	Mitral Valve Regurgitation
						CO	CI	Pressures (mm. Hg)				Resistances (dynes/sec./cm. ⁻⁵)			
								"PVC"	MPA (systolic/diastolic)	MPA (mean)	RV (systolic/diastolic)	Pulmonary Arteriolar	Total Pulmonary		
E. B.	Since patient can remember	AF	RVH	+++	2.1	1.4	?	$\frac{62-70}{30-40}$	53	$\frac{62-72}{4-10}$?	1940	5.2
A. G.	1 mo.	6 mo.	AF	RVH	+++	2.8	1.8	28	$\frac{70-85}{34-48}$	45	$\frac{62-80}{0}$	486	1285	3.5	+++
P. A.	6 yr.	AF	RVH	+++	2.7	1.6	20	$\frac{85}{33}$	48	$\frac{85}{10}$	825	1411	5.4	++++
F. W.	4 yr.	AF	IRBBB RVH	+++	2.2	1.3	13	$\frac{52-58}{16-20}$	33	$\frac{49-57}{0-2}$	727	1200	3	+++
D. R.†	7 yr.	AF	RVH RVH IRBBB	++++	3.2	2.4	3	$\frac{50}{20}$	28	$\frac{48}{0}$	626	700	5	+++

NOTE: RVH = Right ventricular hypertrophy.

LVH = Left ventricular hypertrophy.

IRBBB = Incomplete right bundle branch block.

CO = Cardiac output.

CI = Cardiac index.

PVC = Pulmonary venous capillary mean pressure.

MPA = Main pulmonary artery.

RV = Right ventricle.

* As judged from a left anterior oblique or left lateral view of the chest roentgenogram.

† For discussion of this additional patient see p. 201.

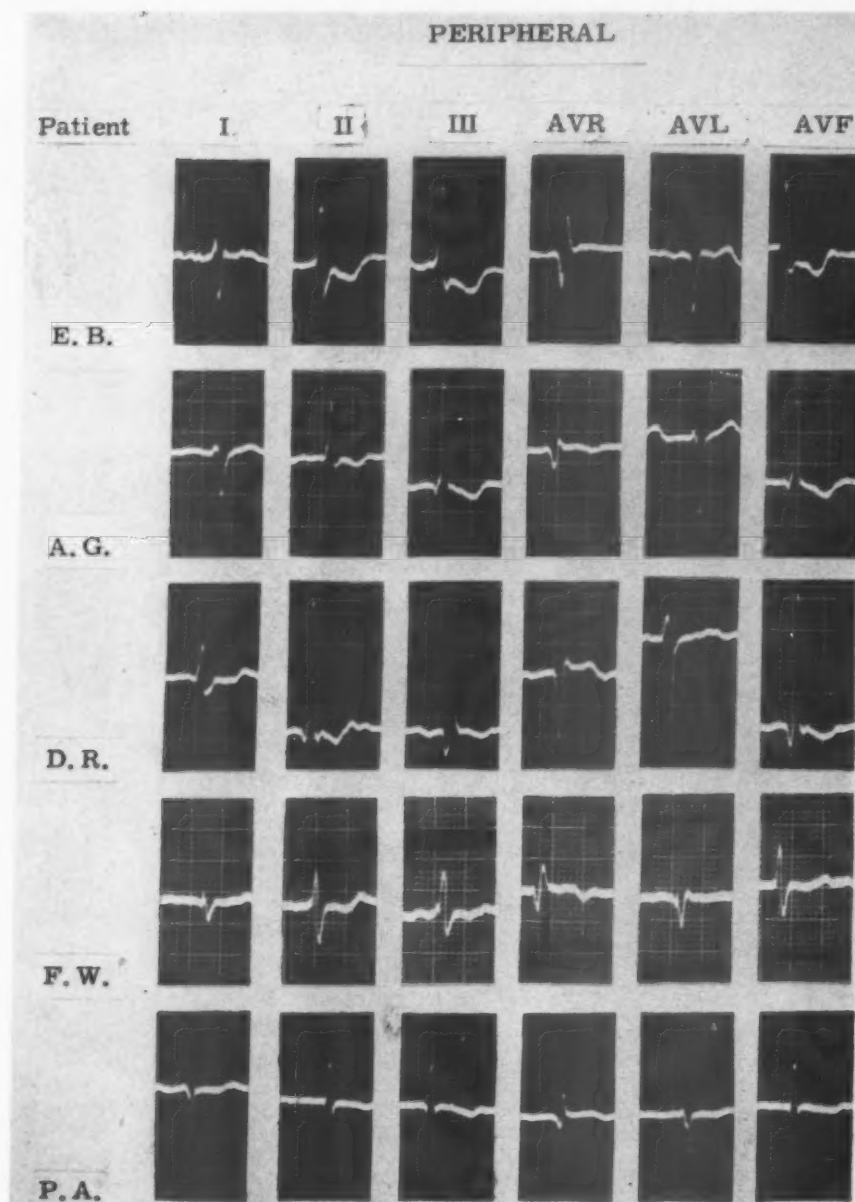


FIG. 1. Peripheral leads in five patients with rheumatic mitral regurgitation. Atrial fibrillation is present in each.

minute with an average of 2.45 L./minute and a cardiac index ranging from 1.3 to 1.8 L./minute/m² with an average of 1.52 L./minute/m² (normal 3.1 ± 0.5 L./minute/m²). The "PVC" ranged from 13 to 28 mm. Hg in three of four patients in whom it was recorded, with an average of 20 mm. Hg (normal 6 to 12 mm. Hg). Pulmonary arteriolar resistance (R) ranged from 486 to 825 dynes/second/cm.⁻⁵, with an average of 679 in three patients. Total pulmonary resistance (R') varied between 1200

and 1940 dynes/second/cm.⁻⁵ with an average of 1459 dynes/sec./cm.⁻⁵ (normal 100 to 150 dynes/second/cm.⁻⁵).

PATHOLOGY

The necropsy data in the two cases in which autopsy was obtained are limited chiefly to the description of the vascular pathology. The pulmonary capillaries were engorged and both arterioles and veins showed intimal thickening with narrowing of the lumen. (Fig. 4.) Small and

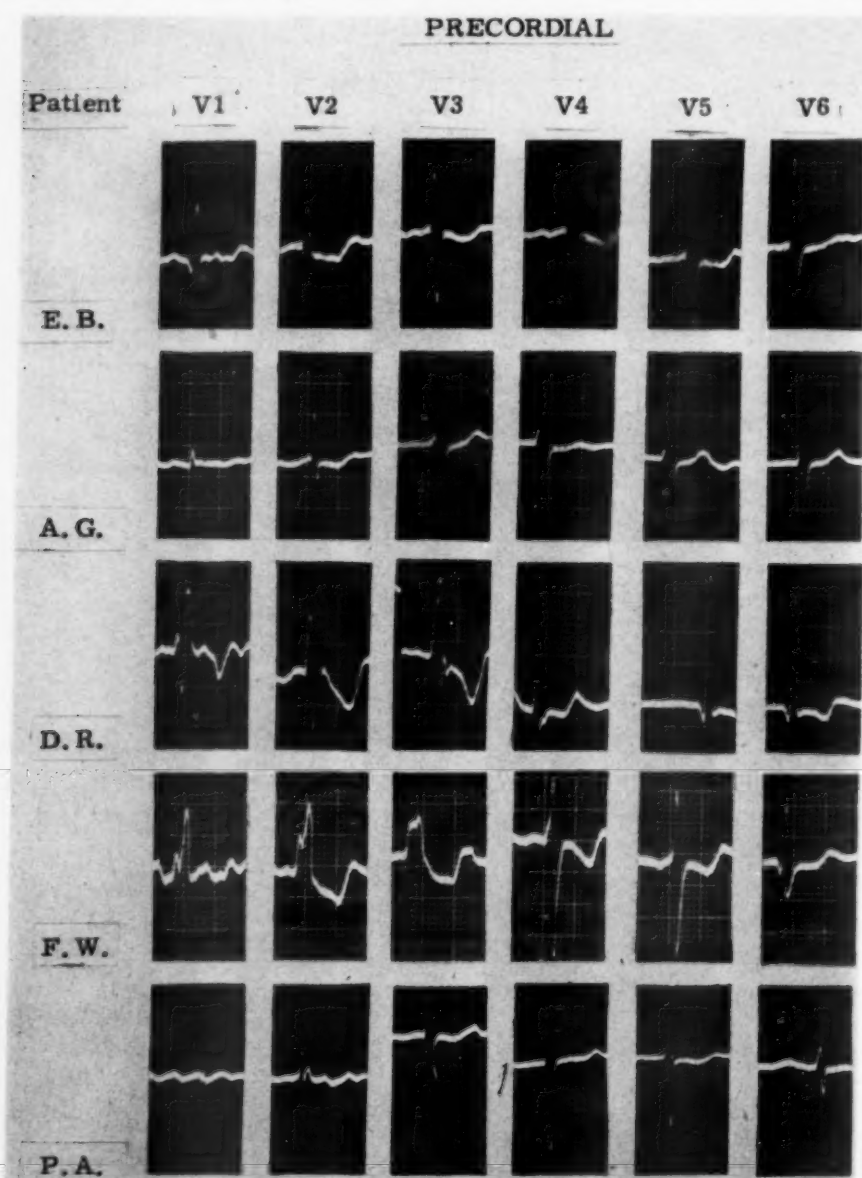


FIG. 2. Precordial leads of five patients with rheumatic mitral regurgitation. Four patients show right ventricular hypertrophy and one (D. R.) shows combined ventricular hypertrophy. Right bundle branch block is noted in two patients (F. W. and D. R.).

large muscular arteries showed marked hypertrophy of the media with frequent evidence of increased connective tissue proliferation. (Figs. 4, 5, 6 and 7.) Marked intimal thickening with fibrosis and cellular infiltration was a frequent finding. (Figs. 4, 5 and 6.) Thickening of the media seemed to prevail in the large muscular arteries. (Fig. 7), while intimal thickening was prevalent in the small ones. (Figs. 5 and 6.) These findings are in keeping with previous re-

ports on the pulmonary vascular changes in mitral stenosis and insufficiency [12,13].

COMMENTS

The four patients represent interesting exceptions to the generalization that significant, isolated mitral insufficiency, which produces an increased left ventricular volume load, ultimately causes enlargement of that chamber alone.

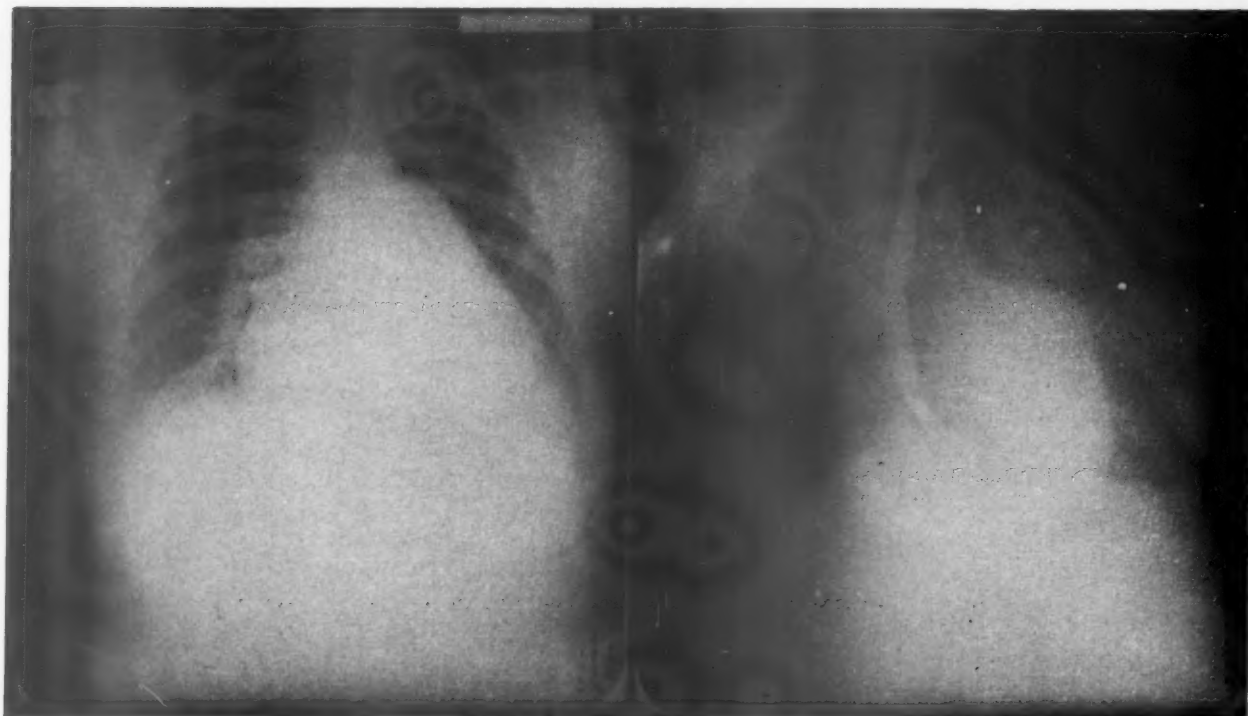


FIG. 3A. Roentgenogram of the chest (Patient P. A.) demonstrating 3-plus enlargement of the heart with considerable right ventricular hypertrophy and prominence of the pulmonary artery segment. There is 2-plus enlargement of the left atrium.

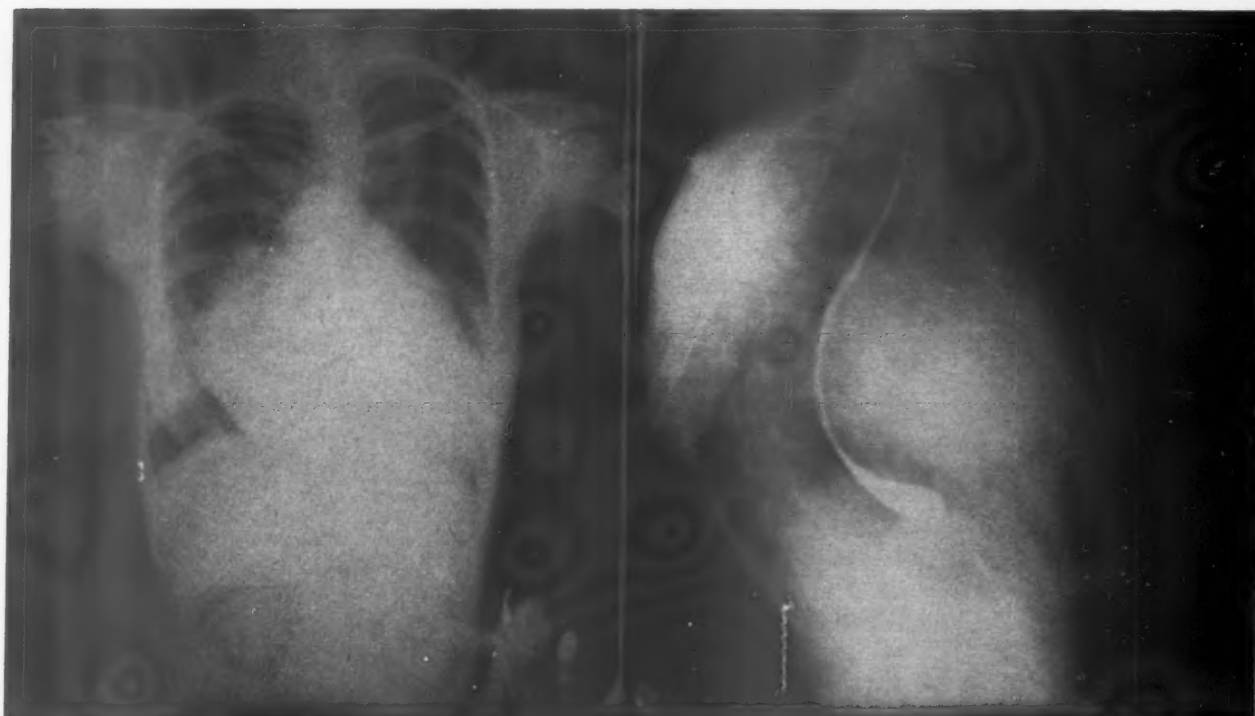


FIG. 3B. Roentgenogram of the chest (Patient D. R.) demonstrating 4-plus enlargement of the heart. Note marked dilatation of the left atrium.

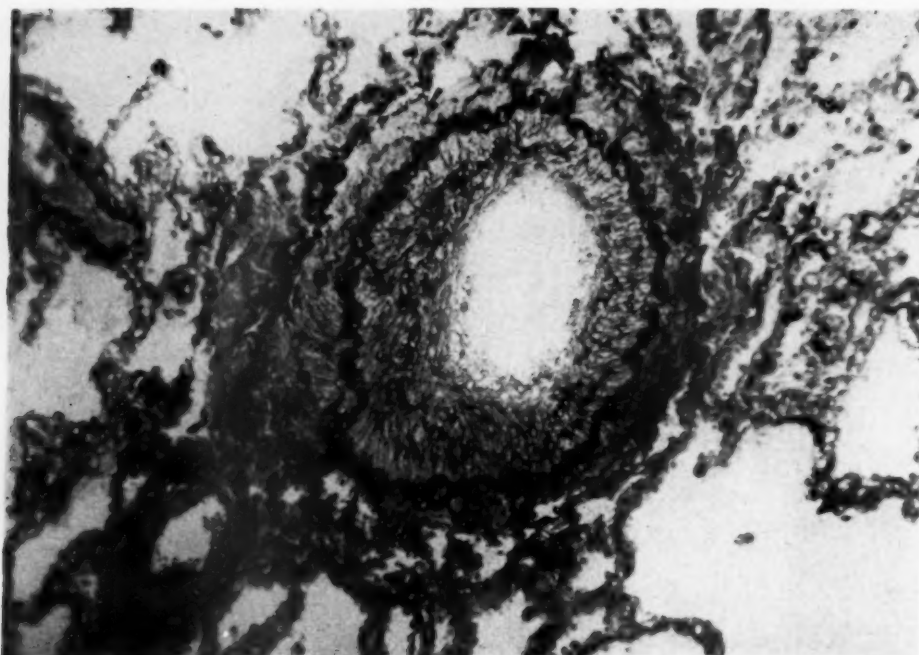


FIG. 4. Photomicrograph of a pulmonary arteriole and venule showing fibrosis with narrowing of the lumen. The central pulmonary artery reveals both medial hypertrophy and intimal fibrosis.

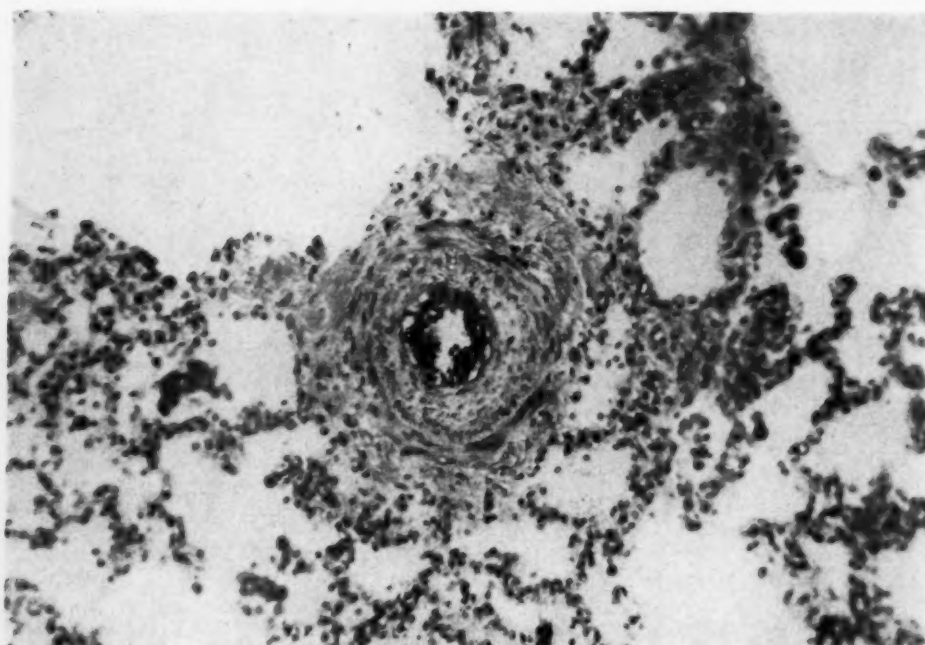


FIG. 5. Photomicrographs of small pulmonary arteries. Note marked intimal proliferation. Marked perivascular fibrosis is present.

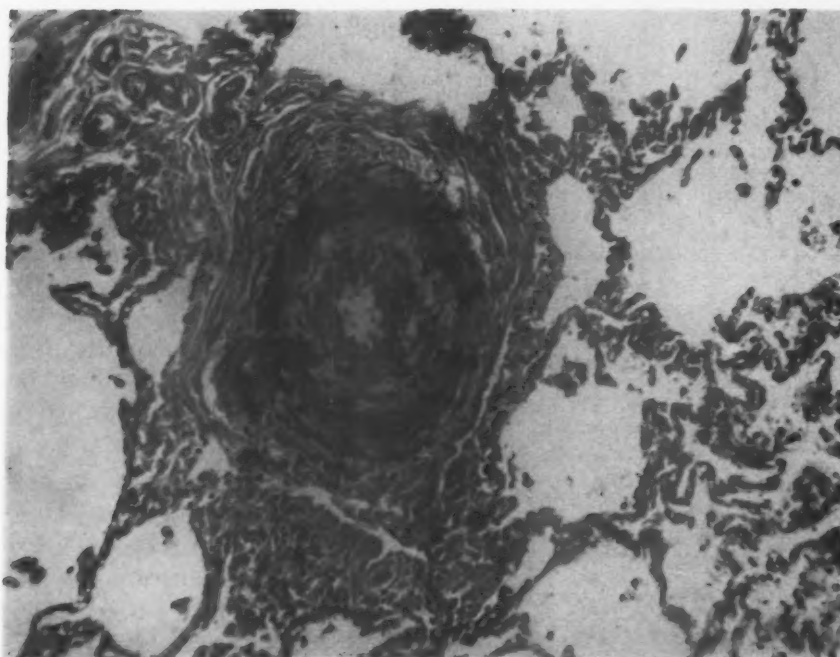


FIG. 6. Photomicrographs of small pulmonary arteries. Note marked intimal proliferation. Marked perivascular fibrosis is present.

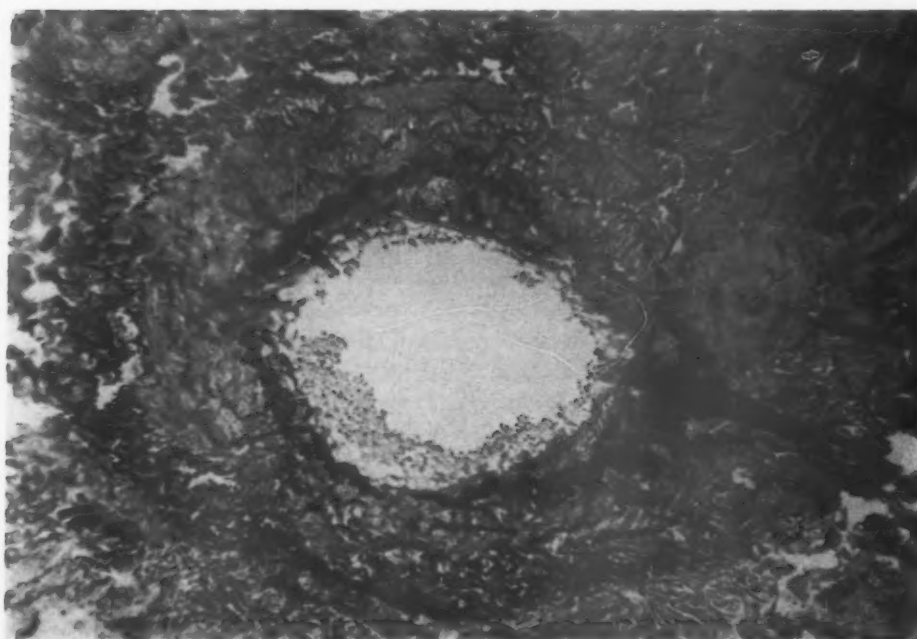


FIG. 7. Photomicrograph of large pulmonary artery. There is marked medial hypertrophy. Verhoeff's elastic tissue stain clearly demonstrates the internal and external elastic lamina.

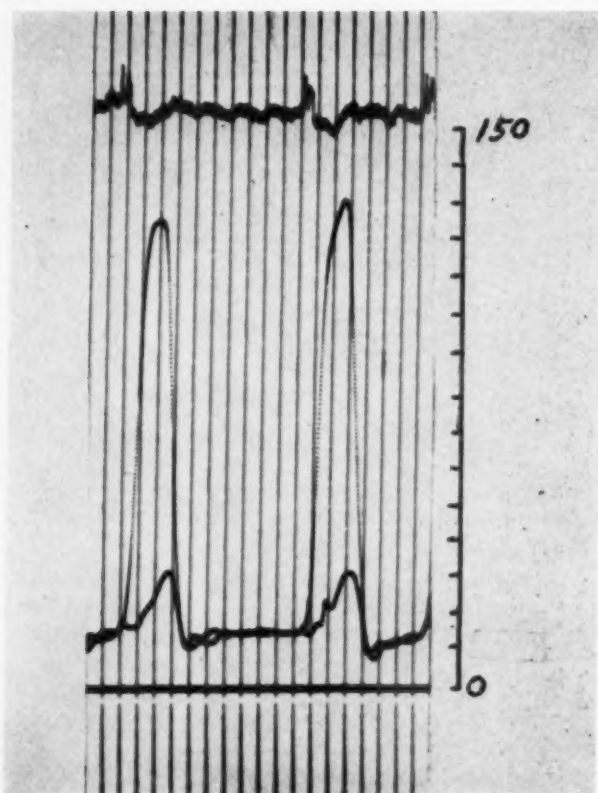


FIG. 8. Simultaneous left atrial and left ventricular pressure tracing in mitral regurgitation. Note prominent C-V wave in left atrial curve, measuring 30 mm. Hg.

The magnitude of the insufficiency in each of the patients implied that the previous rheumatic activity had been quite severe. However, it has been suggested that extreme insufficiency may develop after a mild process because of the peculiar anatomic relation between the endocardium of the posterior-inferior left atrium and the posterior mitral leaflet [9]. According to this mechanistic explanation the dilatation of the left atrium which arises with initial inability of the leaflets to coapt exerts traction on the posterior cusp thereby exaggerating the degree of valvular incompetence and initiating a vicious cycle.

Regardless of how the insufficiency came to pass it is clear that no other valve lesion was present to explain the unusual right ventricular enlargement. The surgical explorations and autopsies specifically eliminated the possibility of mitral stenosis. These examinations revealed no evidence of past or present commissural fusion. Finally, the actual valve area were estimated to range from 3 to 5.4 cm², which is

well beyond the values seen in significant stenosis.

A cogent explanation for the right ventricular enlargement did appear in the catheterization studies which indicated a marked resistance to pulmonary blood flow and in the pathologic review which revealed medial hypertrophy and intimal proliferation in both the large and small arteries of the lungs. The very pertinent question arises as to the manner in which these pulmonary vascular changes became major sequellants and transcended in importance the more usual left ventricular pathophysiology.

In the usual case of mitral insufficiency, when the left ventricle ejects a high velocity column of blood into the atrium the pressure within the latter chamber rises during systole and, if normal rhythm prevails, in late diastole at the time the atrium contracts against its augmented volume load. Thus the fundamental characteristics of this pressure curve are the periodic elevations in systole and the return to normal levels during most of diastole. (Fig. 8.) The amplitude of these pressure peaks is regulated by the volume of the regurgitated stream, by the velocity of its flow and by the distensibility of the atrial muscle. The volume-pressure relationships within the atrium are such that when the volume is constant the pressure level varies inversely with the distensibility of the myocardium [10].

Because of the continuity of the structures, atrial pressures are reflected in the pulmonary vessels. It is reasonable to suggest that pulmonary vascular changes develop either when the pressure elevation is constant rather than intermittent or when the magnitude of the systolic pressure is grossly exaggerated. The maturation of pulmonary vascular pathology is a slow process which usually lags behind the physiologic deterioration of the left ventricle. If the competence of this chamber is impaired because of fibrosis due either to previous rheumatic endocarditis or to coronary insufficiency the clinical picture of the left heart failure will predominate early.

If these concepts are correct it should be possible to demonstrate in the four patients presented a single factor responsible for a persistent elevation in atrial pressure or for a markedly exaggerated phasic pressure. Coexistent mitral stenosis has been eliminated as a possibility. Left heart failure produces a rise in left atrial pressure as a result of increased resistance to left ventricular filling, and theoretically could have been

responsible for producing an ultimate pressure load on the right ventricle. However, this explanation must be abandoned in view of the fact that pre-existing left ventricular enlargement and failure was never observed in these patients.

Any mechanism which is responsible for isolated right ventricular enlargement in mitral insufficiency must exaggerate the left atrial systolic pressure prior to and independent of the occurrence of left ventricular failure. This can develop if we are permitted to believe that the tonicity of the atrial myocardium may be preserved or actually enhanced under certain circumstances, such as hypertrophy. When this muscle fails to "stretch" in response to its augmented volume load, the pressure within the chamber must rise disproportionately. This exaggerated response is transmitted to the pulmonary circuit where it provides an effective stimulus for hypertrophy and fibrosis of the vascular wall. In brief, a tonic atrium may transfer the physiologic burden of mitral insufficiency from the left to the right ventricle through its effect on the pulmonary vascular tree.

This is demonstrated by an additional patient (D. R.) in whom the mitral valve area and degree of regurgitation were similar to those recorded in the four patients presented. (Table 1.) Left ventricular failure had been observed for seven years in this patient, but there was no evidence of right heart failure. The electrocardiogram showed combined left and right ventricular hypertrophy. (Figs. 1 and 2.) X-ray examination revealed massive left atrial enlargement. (Fig. 3B.) The cardiac output was within normal limits and the pulmonary artery pressure and total resistance were considerably less than the values encountered in the four patients under discussion. Of greatest importance, the pulmonary venous capillary pressure was within normal limits. It is postulated that because of the distensibility of the left atrium the phasic pressures within that chamber were not exaggerated. Therefore, no stimulus arose for the development of rapid pulmonary vascular changes, and the left ventricle, continuously exposed to increased volume loads, eventually failed.

Myocardial fibrosis as the result of previous rheumatic activity could be responsible for transformation of the tonic left atrial wall into a passive, highly distensible structure. Undoubtedly, the characteristics of the left atrium play a

most important role in conditioning the type of devolutionary pattern in rheumatic mitral insufficiency.

CONCLUSIONS

1. Four patients are presented in whom isolated mitral insufficiency was accompanied by predominant right ventricular enlargement.

2. It is reasoned that this paradox can arise after significant increase in pulmonary resistance.

3. Exaggeration of the systolic pressures within the left atrium may constitute an adequate stimulus for the development of pulmonary vascular changes in rheumatic mitral regurgitation.

4. The pathophysiologic characteristics of the left atrium and left ventricle are major factors regulating the clinical picture in rheumatic mitral regurgitation.

5. The contribution of the left atrium to the natural history of rheumatic mitral regurgitation is further illustrated by a fifth case which demonstrated the more usual combined ventricular hypertrophy and the clinical picture of left heart failure.

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Localization of Left-to-Right Cardiac Shunts by Dye-Dilution Curves Following Injection into the Left Side of the Heart and into the Aorta*

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THE technic of catheterization of the right side of the heart with sampling of blood from the venae cavae, right atrium, right ventricle and pulmonary artery is the method generally employed in the detection and localization of left-to-right intra- and extracardiac shunts [1]. An increase in the oxygen content of blood obtained as the catheter is advanced from one chamber to the next is attributed to the admixture of oxygenated blood shunted from the left side of the heart. However, the information obtained by this well established diagnostic method not infrequently is inconclusive or false [2]. Diagnostic errors relate to incomplete mixing of blood in the venae cavae and in the

right atrium [2-4], to the incomplete mixing of shunted and non-shunted blood, and to variations in the patient's physiologic state during the period of time required for complete sampling.

An increasing number of patients with left-to-right shunts are being operated upon. The need for improved technics for the detection and precise localization of such shunts is an urgent one since intelligent surgical planning requires accurate preoperative evaluation. In an effort to provide such technics, the efforts of this clinic have been extended in three principal directions. The application of contrast radiography with left ventricular and aortic injections, and the nitrous oxide test are being reported else-

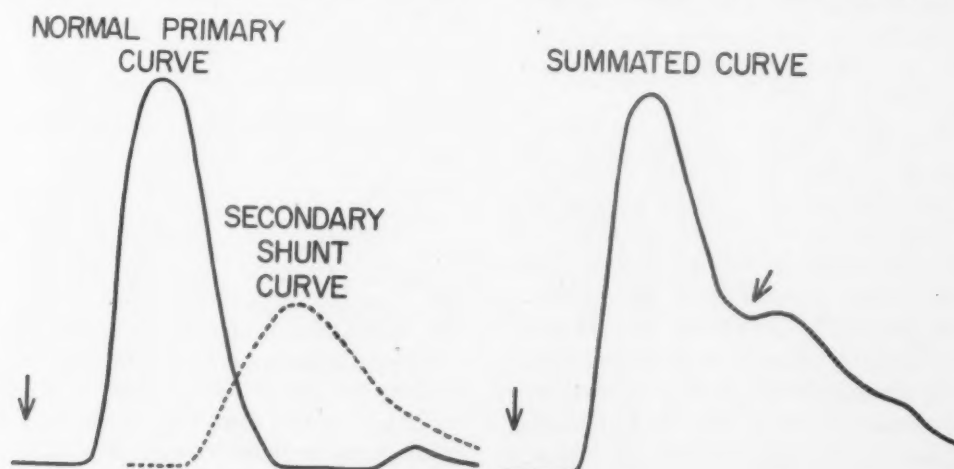


FIG. 1. Theoretic indicator-dilution curves resulting from injection into the left side of the heart. Left, vertical arrow indicates the midpoint of injection. The solid line represents the normal indicator-dilution curve resulting from injection into the left side of the heart or into the aorta. The broken line represents the secondary indicator-dilution curve and relates to that portion of the indicator which has been shunted through the pulmonary circulation. Right, dilution curve representing the sum of the primary and secondary curves following injection of indicator into the left side of the heart proximal to origin of a left-to-right shunt.

* From the National Heart Institute, Bethesda 14, Maryland.

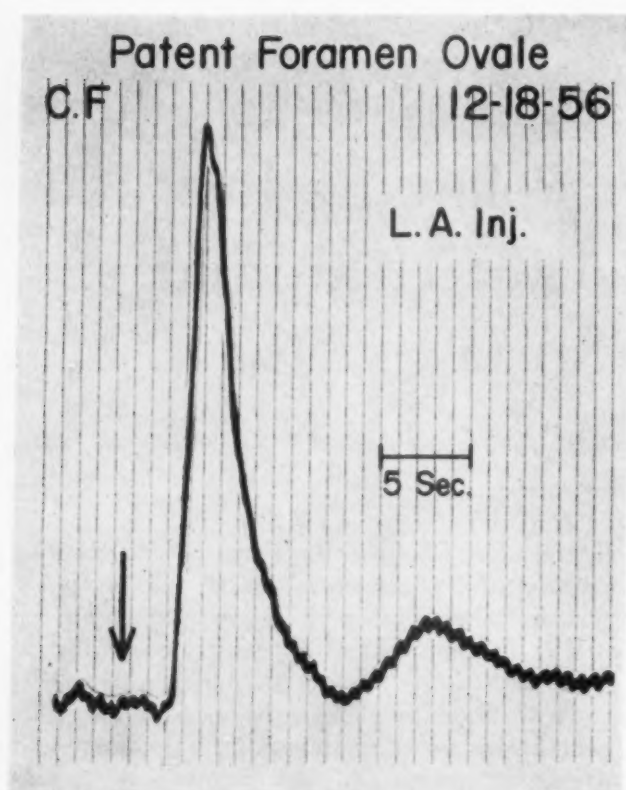


FIG. 2. Case 1. Normal dye-dilution curve following injection into the left atrium in a patient with a non-shunting patent foramen ovale. Vertical arrow indicates the mid-point of injection. Time lines = 1.0 second.

where [2,5]. Wood, Swan and their collaborators have pioneered in developing a wide variety of techniques utilizing indicator-dilution curves in the diagnosis of congenital cardiac malformations [5b].

Right-to-left shunts may be localized by the rapid injection of an indicator into the right side of the heart and by the recording of dilution curves from a systemic artery [6]. This technic has also been valuable in the detection of left-to-right shunts which exceed 20 per cent of the pulmonary blood flow [7]. However, its value in the exact localization of such shunts has been limited to the detection of partial anomalous pulmonary venous drainage [8]. The development of techniques for catheterization of the left side of the heart and central aorta permit the injection of indicator substances into these areas. The resulting dilution curves recorded from a peripheral artery or from the heat-flushed ear have made the precise localization of left-to-right shunts possible [9a,9b]. The present report deals with this technic and its applications in a total of eighty patients.

THEORY

Following the rapid injection of an indicator into a pulmonary vein, the left atrium, left ventricle or central aorta of a normal subject, the dilution curve recorded from a systemic artery exhibits a rapid, sharp ascent and a slightly slower, smooth, uninterrupted descent. (Fig. 1.) The primary curve returns to the baseline before the appearance of normally recirculated indicator. When the injection is made proximal to a left-to-right shunt, a fraction of the indicator is shunted across the defect, through the lungs and then returns to the left side of the heart. A progressively decreasing quantity of the indicator continues to be shunted through the pulmonary circulation. The dilution curve resulting from an injection proximal to a left-to-right shunt is the sum of two components. The first component results from that portion of indicator which follows the normal circulatory path and is manifested in the rapid ascent and beginning descent of the dilution curve. The second component results from the delayed appearance in the systemic circuit of that portion of indicator which has been shunted from left-to-right and through the pulmonary circulation. This delayed appearance of indicator interrupts the descending limb with a secondary peak or abrupt change in slope. The continuation of recirculation is seen as a gradually falling concentration with failure of the curve to return to the baseline. In contrast, when the indicator is injected distal to rather than proximal to the origin of the left-to-right shunt, a normal curve results. Thus, the selective injection of indicator into various areas of the left side of the heart or of the aorta can serve to demonstrate the presence and can localize the origin of left-to-right shunts.

PATIENT MATERIAL AND TECHNIQS

A total of eighty patients were studied. In forty-seven of these the presence or absence of a left-to-right shunt was determined at operation, in ten by selective aortography and in the remaining twenty-three by the application of the nitrous oxide test during catheterization of the right side of the heart [2], as suggested by Callaway. Catheterization of the left side of the heart was generally performed by the trans-bronchial route, the details of which have been described [10]. In eleven patients at the time of catheterization of the right side of the heart, the catheter was manipulated into the left side of the heart, either across an inter-atrial septal defect or through a catheter-patent, non-shunting, foramen ovale. The central aorta was catheterized either through a No. 12 thin-walled needle introduced percutaneously into the femoral artery [11] or through the surgically exposed ulnar artery.

The concentration of indicator dye was usually continuously measured in peripheral arterial blood by withdrawal of blood through a cuvette densitometer

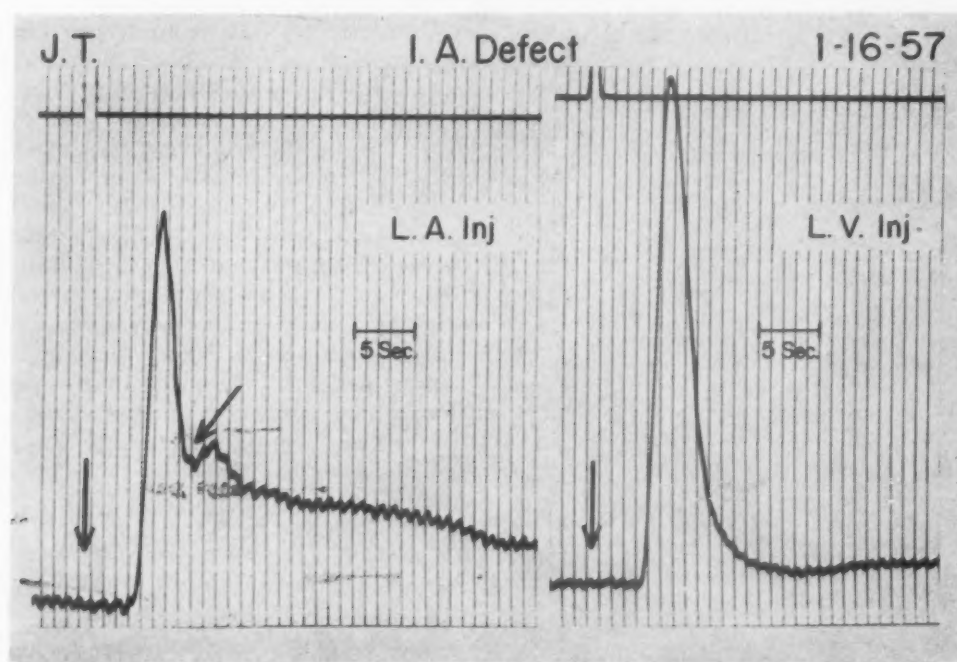


FIG. 3. Case II. Abnormal dye-dilution curve following injection into the left atrium (left) and normal curve following injection into the left ventricle (right) in a patient with an interatrial septal defect.

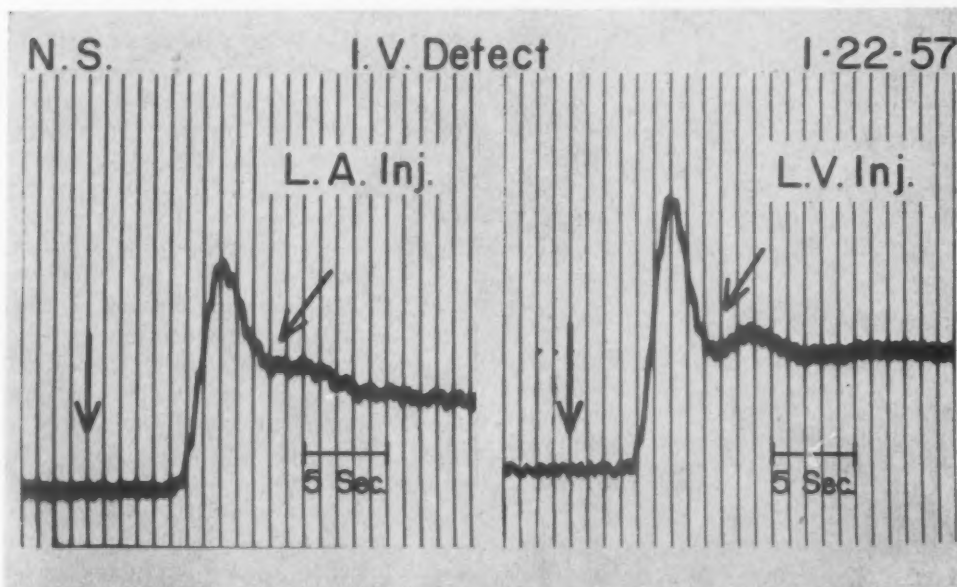


FIG. 4. Case III. Abnormal dye-dilution curves following injections into the left atrium (left) and into the left ventricle (right) in a patient with an interventricular septal defect.

[12] by means of a constant rate, motor-driven syringe. In order to obviate arterial cannulation in infants and small children, curves were often obtained with an oximeter [13] from the heat-flushed, arterialized ear. Time-concentration curves were recorded with a photographic, cathode-ray instrument. Evans blue or indigo carmine were the indicator dyes employed. The latter substance may be administered repeatedly without discoloration of the skin or mucous membranes [14].

FEBRUARY, 1958

RESULTS

There were no complications from the catheterizations of left side of the heart or of the central aorta. The presence or absence of a left-to-right shunt was correctly determined in all patients studied. The dye-dilution curves afforded accurate localization of the shunts in the patients in whom the exact site of the shunt was proved at operation or by means of aortography.

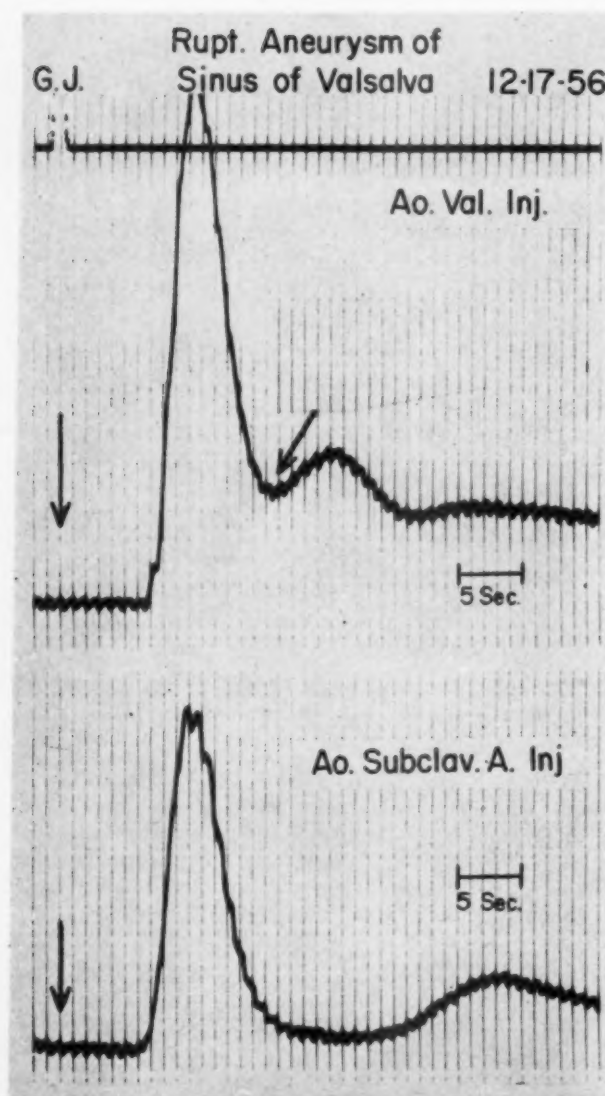


FIG. 5. Case IV. Abnormal dye-dilution curve following injection into the aorta just above the aortic valve (upper) and normal curve following injection into the aorta at the level of the left subclavian artery (lower) in a patient with a ruptured aneurysm of the sinus of Valsalva.

Applications of the technic are illustrated in the following cases.

CASE REPORTS

CASE I. C. F., a three and a half year old girl had valvular pulmonic stenosis demonstrated at catheterization of the right side of the heart. The catheter could be advanced into the left atrium and the oxygen content of right atrial blood suggested the presence of a left-to-right shunt. However, a dye-dilution curve following left atrial injection was normal (Fig. 2), indicating that the catheter had crossed a non-shunting, patent foramen ovale. This interpretation was confirmed at the time of her operation for pulmonic stenosis.

CASE II. J. T., an eighteen year old boy with an interatrial septal defect had the harsh apical systolic murmur and electrocardiographic configuration suggesting the presence of associated mitral regurgitation [15]. The dye-dilution curve resulting from injection into the left atrium was abnormal, indicating the presence of a left-to-right shunt. (Fig. 3.) The curve following injection into the left ventricle was normal, however, and thus ruled out the presence of a left-to-right shunt distal to the mitral valve. Further, associated mitral insufficiency was also excluded since the regurgitation of blood from left ventricle to left atrium and then across the interatrial septal defect would have resulted in an abnormal curve following the injection into the left ventricle. The presence of an interatrial septal defect without associated mitral insufficiency was confirmed at the time of operation.

CASE III. The curves obtained from J. T. (Fig. 3) may be contrasted to those from N. S., a fifteen year old girl with an interventricular septal defect. The abnormal dilution curve following the injection into the left atrium (Fig. 4) indicated the presence of a left-to-right shunt. The abnormal curve following injection into the left ventricle indicated that the left-to-right shunt originated distal to the mitral valve.

CASE IV. G. J., a thirty-nine year old man had a continuous murmur over the precordium and evidence of a small left-to-right shunt at catheterization of the right side of the heart. The differential diagnosis was between a shunt originating from the aorta at the level of the left subclavian artery (patent ductus arteriosus) and a shunt originating from the root of the aorta (aorticopulmonary window, ruptured aneurysm of the sinus of Valsalva or coronary arteriovenous fistula). The abnormal dilution curve following injection into the ascending aorta indicated that the left-to-right shunt originated distal to the aortic valve. (Fig. 5.) A patent ductus arteriosus was excluded by the normal curve following injection into the aorta at the level of the left subclavian artery. An aneurysm of the sinus of Valsalva with rupture into the right atrium was demonstrated by means of thoracic aortography. This case demonstrates that while dye-dilution curves with injection into the left side of the heart or into the aorta precisely localize the origins of shunts, they do not indicate the site in the right side of the heart or in the pulmonary artery into which blood is shunted.

CASE V. D. W. is a six year old boy in whom dye-dilution curves following injection at the root of the aorta and into the aorta at the level of the left subclavian artery were abnormal, while the curve following injection into the descending thoracic aorta was normal. (Fig. 6.) This indicated that the shunt originated near the level of the left subclavian artery. The diagnosis of patent ductus arteriosus was confirmed at operation.

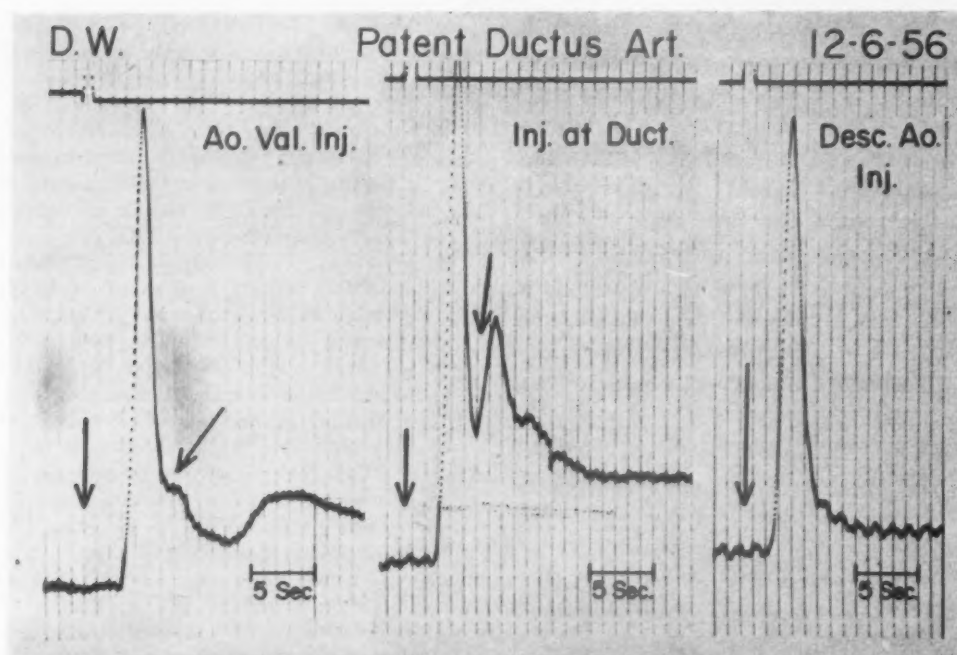


FIG. 6. Case v. Abnormal dye-dilution curves following injections at the root of the aorta (left) and into the aorta at the level of the left subclavian artery (center). Normal curve following injection into the descending aorta (right) in a patient with patent ductus arteriosus.

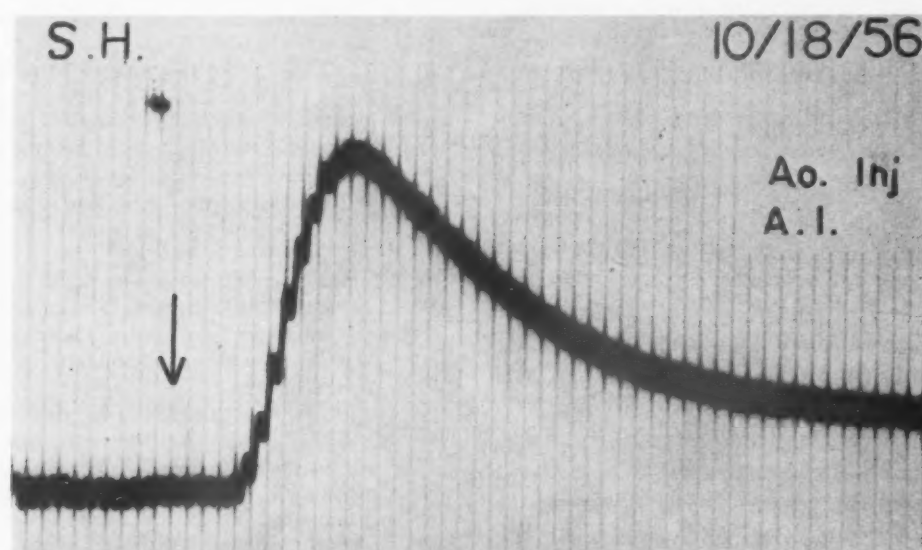


FIG. 7. Case vi. Dye-dilution curve following injection into the ascending aorta in a patient with severe aortic regurgitation.

CASE VI. S. H. was a forty year old woman with Marfan's syndrome without a left-to-right shunt in whom the presence of severe aortic insufficiency was confirmed at postmortem examination. The dye-dilution curve following injection into the ascending aorta was characterized by a normal ascent, but a markedly prolonged, smooth descent uninterrupted by the sudden appearance of recirculating dye. (Fig. 7.) This curve is typical of those obtained in twenty patients with aortic regurgitation following injections into the

left ventricle. This configuration results from repeated regurgitation of a portion of the indicator.

COMMENT

The diagnostic technic described has been of particular value in the preoperative evaluation of patients with left-to-right shunts. Uncomplicated ostium secundum atrial septal defects may be closed without the aid of extracorporeal circula-

tion and with a relatively low operative mortality. In contrast, the closure of an interventricular septal defect or the repair of a persistent common atrioventricular canal requires an artificial heart-lung machine, and the surgical mortality rate is still relatively high. Similarly, the surgical considerations for the closure of a patent ductus arteriosus differ considerably from those for closure of a left-to-right shunt at the aortic root. Accurate diagnosis is therefore essential in the selection of patients and in the planning of operations for the correction of left-to-right shunts.

It is of interest that no curves indicating the presence of a left-to-right shunt were obtained from patients without shunts; correct diagnoses were made in all patients with shunts and no errors in the localization of their origin have thus far been observed. In a series of dogs with a variety of experimental left-to-right shunts the technic was similarly accurate [16]. The sensitivity of the method is reflected in the observations on two patients in whom the correct diagnosis was made by dye-dilution curves, although the shunts were too small to be detected by oxygen differences.

SUMMARY

A technic for the detection and precise localization of left-to-right cardiac shunts is described. It consists of the rapid injection of an indicator dye into the catheterized left side of the heart or into the central aorta and the recording of an indicator dilution curve from a systemic artery or from the heat-flushed ear. In patients without left-to-right shunts the curves consisted of a steep ascent and smooth, rapid descent. When the dye was injected proximal to the origin of a left-to-right shunt the descent of the primary curve was interrupted by the appearance of dye which had been shunted through the pulmonary circulation. Injections distal to the origin of the shunt resulted in normal curves. The technic has been applied in a total of eighty patients. It has proved of particular value in distinguishing: (1) uncomplicated atrial septal defect from atrioventricularis communis or interventricular septal defect; (2) atrial septal defect from partial anomalous pulmonary venous drainage and patent foramen ovale; and (3) patent ductus arteriosus from shunts originating at the root of the aorta.

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Isorhythmic Dissociation

Atrioventricular Dissociation with Synchronization

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IN A-V dissociation and complete A-V block the independence between atria and ventricles is not so absolute as the terms imply. This has been previously emphasized [1]. Indeed, during these dysrhythmias, atria and ventricles may interact in many ways and these were reviewed. One little recognized type of interaction is "synchronization."

In brief, if two tissues with inherent pulsatility are placed in contact, although they lack anatomic continuity, there is a tendency for the two to assume synchronous rhythms. For many years it has been well recognized that such synchronism can develop in apposed nervous tissues, but it was Segers in 1946 who first drew attention to this phenomenon as an attribute of cardiac muscle and provided an experimental background for its understanding [2]. He showed that the phenomenon could develop between isolated fragments of frog's heart, between isolated ventricles, and between atria and ventricles in the presence of experimentally induced complete A-V block. Synchronization was more likely to develop when the rates of impulse formation in the two approximate tissues were not greatly dissimilar, and its development usually resulted solely or mainly from acceleration of the slower partner. When the period of resulting synchronization was short-lived, Segers applied the term "accrochage." His fundamental work has been reviewed in detail [3] and will therefore not be further enlarged upon here.

Synchronization has been described clinically in A-V block [3,4]. In A-V dissociation the phenomenon has been little discussed although the propensity of P waves to cluster in the neighborhood of the QRS complexes is recognized [5]. In the French literature such clustering has been documented under the title "dissociation iso-

rythmique" and Segers has attributed it to A-V synchronization [6]. He regards the phenomenon as very rare, but we question this as we have observed it a number of times during the past

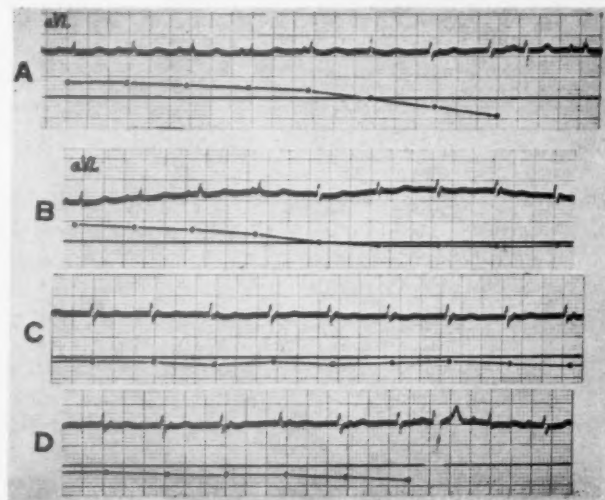


FIG. 1. Two strips of aVL from Case 1. B, C and D are a continuous strip. A shows A-V dissociation without synchronization. B, C and D show A-V dissociation with synchronization (accrochage). As a visual aid to the changing A-V relationship, the P-R and R-P intervals are graphically plotted below the tracing; P-R intervals are plotted as distances above the horizontal line, while R-P intervals are plotted below it.

eighteen months. It is our purpose to focus attention on "synchronized dissociation" and to present a selected group of five tracings which illustrate variations on this theme.

DESCRIPTION OF ELECTROCARDIOGRAMS

CASE 1. The tracing in Figure 1 is from a white girl of fourteen years of age, who was admitted to the Mercy Hospital with acute rheumatic fever. She had received no digitalis,

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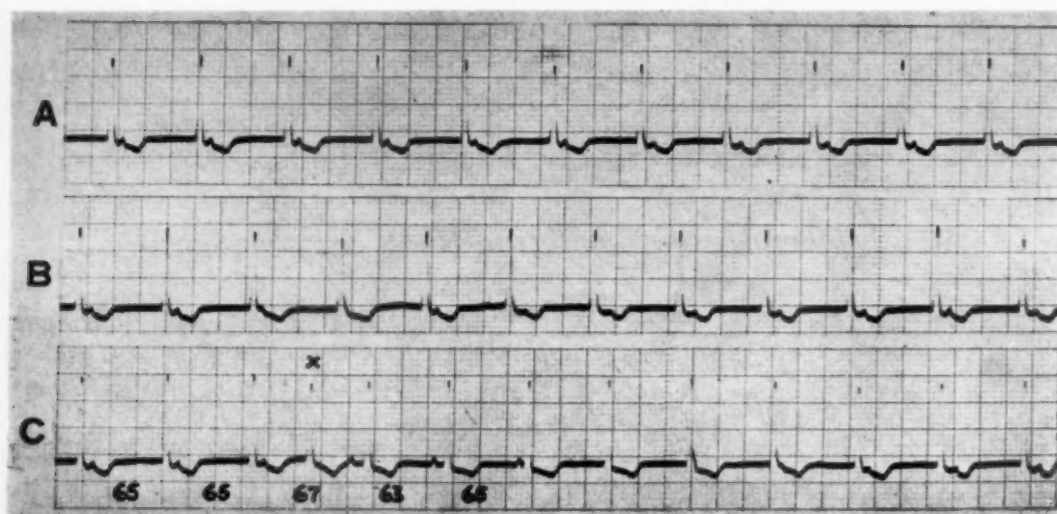


FIG. 2. Three selected strips of lead I from Case II. For description see text.

salicylates or steroids at the time this record was obtained. In strip A the P wave "marches through" the QRS complexes without hesitating. On the other hand, in B, C and D (which form a continuous strip) the P wave, when it approaches the QRS, experiences difficulty in "getting past" it and remains linked closely to it for several cycles. A similar example of synchronization in this same patient has been published elsewhere [7].

CASE II. The tracing in Figure 2 is from a fifty-one year-old Negro man with hypertension who was admitted to the University Hospital with acute pulmonary edema and uremia. He had been taking an unknown maintenance dose of an unknown digitalis preparation and received 1.2 mg. of cedilanid® and 0.2 mg. of digitoxin during his first twenty-four hours in the hospital. Subsequent to this the record illustrated in Figure 2 was obtained and a total of over thirteen minutes of tracing showing A-V dissociation was available from which representative strips were chosen. Most of the time the P waves were postincident, falling closely after the QRS, usually with R-P interval of 0.08 to 0.12 second as shown in strip A, and never increasing beyond 0.18 to 0.19 second. Occasionally the P wave would approximate the QRS and would almost disappear within it, as in the fourth beat of strip B. R-R intervals remained remarkably constant throughout and on only one occasion was their rhythm interrupted by a premature beat (x in strip C). After this beat the P wave precedes the next QRS complex with a normal P-R interval, and indeed this cycle probably represents a conducted beat. Atria and ventricles

then immediately dissociate again and the P wave marches through the QRS complex to become fixedly postincident once more.

Although it is not germane to the present argument, the premature beat (x in strip C), because its nature is not immediately apparent, cannot be allowed to pass without comment. It is clearly of supraventricular form and at first sight one is tempted to regard it as a conducted beat with prolonged P-R interval following the preceding P wave—an "interference" or "capture" beat. But if this atrial impulse so closely following the QRS is conducted, why were not other P waves, with similar or even longer R-P intervals, also conducted? One of the characteristics of A-V dissociation with interference is that the incidence of the conducted atrial impulses is predictable. If it were a nodal premature beat, the atrial rhythm should have been disturbed by the retrograde impulse. But the P waves are evenly spaced—the first five P-P intervals in strip C measure 65, 65, 67, 63 and 65 hundredths of a second. The remaining possibility is that this is one or another of an indistinguishable pair: a nodal premature beat with retrograde block or a main stem extrasystole [7].

CASE III. The tracing in Figure 3 is from a white girl of fourteen years of age, who was admitted to the University Hospital with acute rheumatic fever. At the time the record was obtained she had received 2.6 gm. of aspirin but had not had digitalis or steroids. Strip A shows initially a run of sinus rhythm giving way to A-V dissociation during which the P wave is lost within the QRS. Strips B and C, forming a continuous record, show the effect of a Valsalva

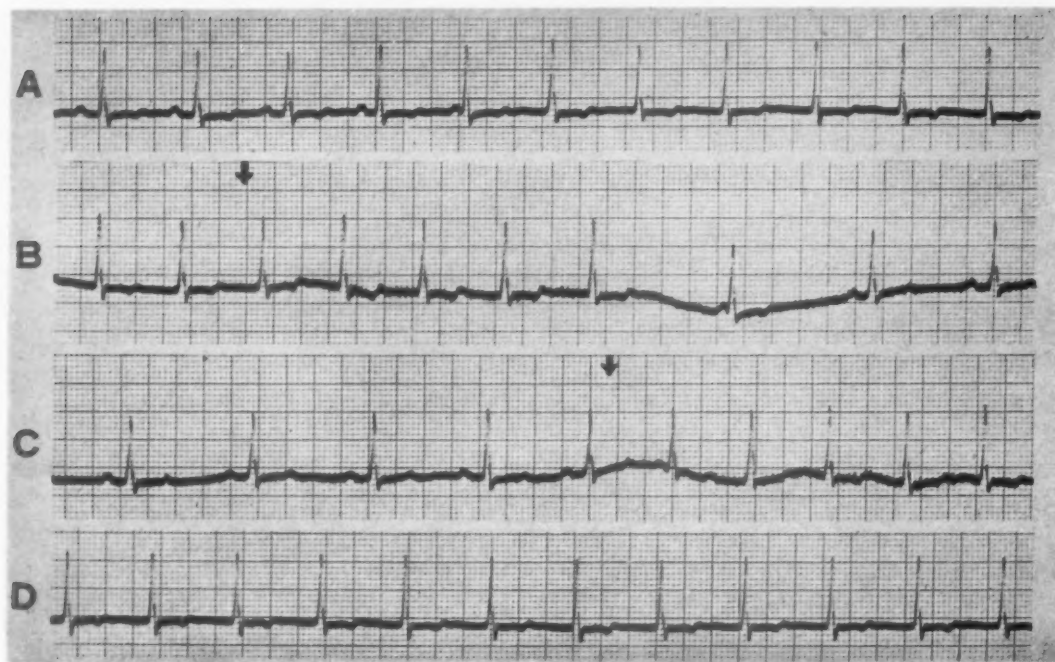


FIG. 3. Selected strips from lead II of Case III. B and C are continuous. Marker in B indicates beginning of Valsalva maneuver; marker in C indicates termination of Valsalva maneuver. For description see text.

maneuver: by slowing both atria and ventricles, but ventricles apparently more than atria, it breaks the synchronized dissociation and temporarily restores sinus rhythm. As soon as the maneuver is over (marker in strip C), atria and ventricles once more dissociate and synchronize. In strip D they remain consistently synchronized. In the whole tracing, which occupied several consecutive minutes, such periods of synchronization were observed lasting twenty, twenty-six, thirty-six, thirty-six, sixty-three and ninety seconds. Four of these were promptly terminated by a Valsalva maneuver; the other two reverted spontaneously to temporary sinus rhythm. One of these two was interesting in that synchronization resisted twelve seconds of a Valsalva maneuver only to terminate spontaneously fourteen seconds later.

CASE IV. The tracing in Figure 4 is from a white boy of six years of age, who was admitted to the Mercy Hospital with acute rheumatic fever. A and B form an almost continuous record—a few beats are missing between them. In A, after three sinus beats, A-V dissociation develops with the ventricles under ectopic rather than nodal control; dissociation continues in B until the S-A node regains control for the last five beats. In C dissociation is constant with the P wave consistently situated just beyond the QRS. During the short periods of dissociation illus-

trated, the P waves clearly tend to remain "linked" to the ventricular complexes. That this is more than mere chance is suggested by the fact that the P-P intervals are much more constant during the periods of apparent linkage than during sinus rhythm or during dissociation before linkage occurs. In the whole strip of V₁, there were seventy-nine P-P intervals available for measurement. Of these, twenty-eight occupied periods in which linkage was evident, and for these the P-P intervals ranged only between 0.60 and 0.64 second; on the other hand fifty-one P-P intervals in stretches that did not show linkage ranged between 0.51 and 0.72 second, indicating an inherent sinus arrhythmia. This suggests that the A-V attachment was more than fortuitous and represented true accochage.

CASE V. The tracings in Figures 5 and 6 are from a white man of twenty-three years of age, who was admitted to the Mercy Hospital with a subarachnoid hemorrhage but with no evidence of heart disease. In Figure 5, strip A shows constant sinus rhythm with sinus arrhythmia. In B the first three beats are normal sinus beats, but the last three show ventricular escape, fusion beats resulting. Strips C, D and E are continuous. In C and D the P waves flirt with the QRS complexes so that variegated fusion beats result. An occasional sinus beat (first beat in C, fifth in D)

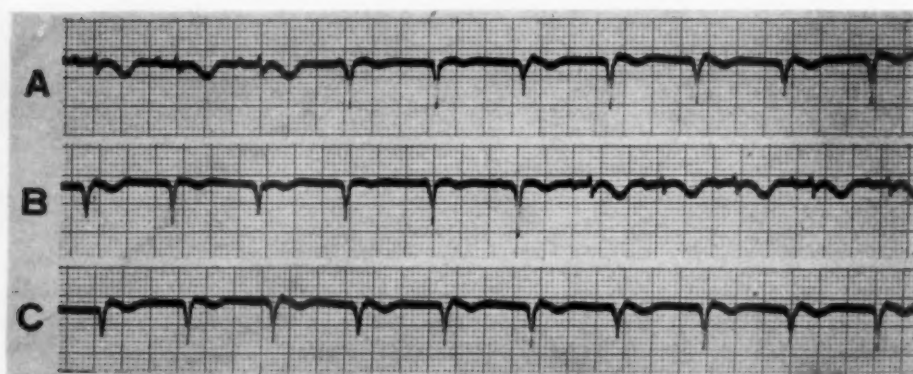


FIG. 4. Selected strips from lead V_1 of Case IV. For description see text.

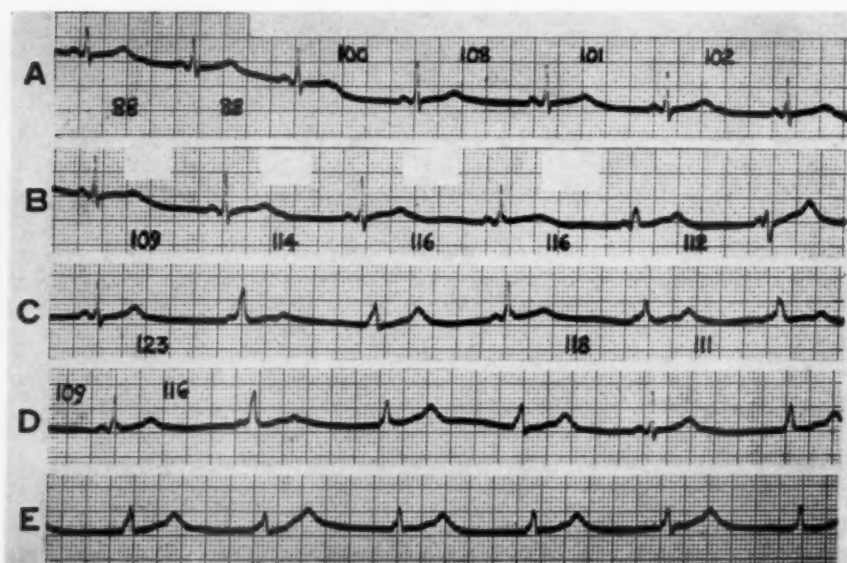


FIG. 5. Five selected strips of lead II from Case V. C, D and E are continuous. P-P intervals are indicated in hundredths of a second on the tracings. For description see text.

is seen; between them are beats showing minimal summation effects (fourth beat in C and first in D), and some that presumably represent complete ventricular escape (third in C, fourth in D). In E there is constant dissociation with synchronization.

In aVR of Figure 6 the first two beats are sinus beats. The third beat is a fusion beat representing partial ventricular escape. The remaining beats show A-V dissociation with the P wave gradually disappearing into the QRS complex. Throughout aVL the P waves remain synchronized with the QRS complexes. In aVF two sinus beats are followed by one fusion beat and then ventricular escape occurs with A-V synchronization.

Of 151 R-R intervals available for measurement, all measured 112 ± 1 hundredths of a second. On the other hand, of the thirty-four clearly measurable P-P intervals, the range was

88 to 123 hundredths. Thus, whenever there is a sequence of visible P waves they are seen to be irregular. Indeed it is this inherent sinus arrhythmia that permits the development of A-V dissociation by default—when the sinus interval becomes unduly long, ventricular escape occurs. With such escape the ventricular rhythm becomes absolutely regular and the P waves remain buried in the rhythmic QRS complexes and must therefore themselves be regular. In other words, when the S-A node is left to its own devices it is arrhythmic; but when its impulse coincides with an independent ventricular impulse, it is apparently regulated by it, until it manages to break the bond by initiating an early beat.

COMMENTS

Some authors have published examples of A-V dissociation which show brief periods of

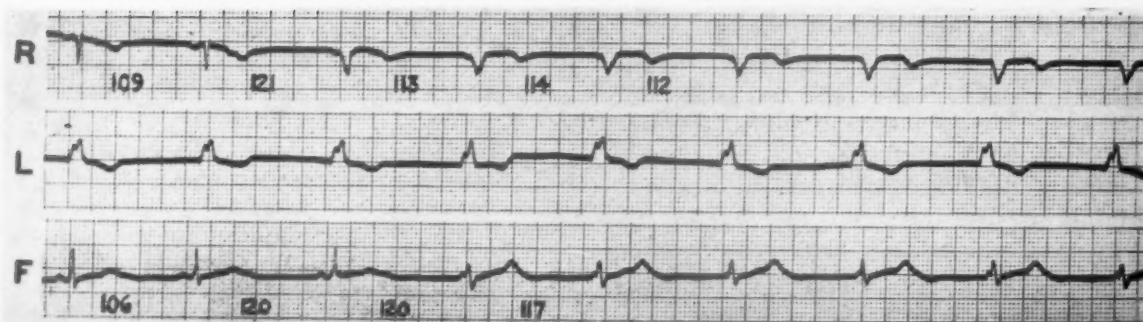


FIG. 6. The unipolar leads from Case v. P-P intervals are indicated in hundredths of a second on the tracings. For description see text.

possible synchronization without commenting on the phenomenon [8-10]. On the whole such tracings are too short to exclude the possibility of coincidence rather than true accrochage. On the other hand, others observed the tendency of atria and ventricles to synchronize during dissociation without publishing the tracings concerned. Kaufmann and Rothberger [11], for example, make comment in the following terms: "The oscillating sinus and ectopic rhythms find each other again and unite for short stretches in a simple relationship . . . one must postulate a surprising sort of pre-stabilized harmony between the normal focus in the sinus and ectopic focus in the A-V node or ventricle." Van Buchem [12] described a tracing of A-V dissociation in which, whenever the P wave reached a distance of 0.19 second after the onset of the QRS, the atria accelerated to match the ventricular rate and this R-P interval was then maintained. Rivoalen and associates [13], again without publishing the illustrative records, reported five examples of isorhythmic dissociation occurring in rheumatic fever and expressed the opinion that this phenomenon was much more common than was previously thought.

Of those who have both observed and commented on the phenomenon and also published tracings illustrating it, Gallavardin and associates [14] were apparently first. As long ago as 1914 they reported the production of A-V dissociation by ocular pressure and noted that the postincident P waves remained synchronized with the T waves. In another experiment A-V dissociation was produced by atropine, and the postincident P waves preserved a stable relationship to the ventricular complexes. In 1928 Gallavardin and Veil [15] published a single further example; they gave no name to the phenomenon but described the A-V relationship as "disjonction auriculo-ventriculaire sans dis-

sociation." In 1934 Enescu and Vacareanu [16] published two cases and introduced the term "dissociation isorythmique." They stated that the phenomenon was very rare and that the only previously reported cases known to them were those of Gallavardin. Risotto and co-workers [17] reported no less than twenty-six examples of A-V dissociation complicating diphtheria; of these, seventeen were considered to show an isorhythmic tendency and twelve of these were illustrated. More recently Grant [5] drew attention to this form of A-V synchronization and published an illustrative tracing.

In none of these cases, including ours, can the presence of synchronization be proved. The various patterns of isorhythmic dissociation seen, however, can be said to suggest its presence with varying degrees of probability. If for a few beats the dissociated atrial and ventricular pacemakers fall in step, synchronization is a possibility and may be suspected. (Case I.) If repeated periods of such spontaneous synchronism are observed, or if disrupting influences (such as a premature beat or a Valsalva maneuver) are followed by prompt return to the synchronized relationship, this constitutes stronger evidence for synchronization. (Cases II and III.) An even stronger measure of probability is afforded by the observation that, when the two impulses approximate, one pacemaker surrenders a feature of its identity, for example, an inherent arrhythmia. (Cases IV and V.)

From the limited number of tracings of isorhythmic dissociation available for scrutiny, it would appear that as a rule the atria surrender to the rhythm of the ventricles. This is in keeping with Segers' observation *in vitro* that the slower beating fragment or chamber usually accelerated to keep pace with the faster beating chamber. It is also noticeable that the synchronizing atrial impulse tends to attach itself just behind the

QRS complex rather than in front of it. The P wave gets past the QRS but cannot stray far beyond it. (Cases I, II and IV.) This tendency calls to mind the repeated hypothesis [18,19] that ventricular contraction can produce a mechanically stimulating effect on the formation of the sinus impulse and makes one wonder if at least this pattern of synchronization is not mediated by a purely mechanical influence. This is in harmony with Segers' observation that synchronization between ventricles *in vitro* could be induced by mechanical means alone [2].

On the other hand Segers also clearly showed that when mechanical interaction was eliminated, synchronization could be effected by electrical influences alone [2]. On the electrical side Grant [5] has ingeniously compared the operation of independent sinus and nodal pacemakers with an experimental pair of coupled oscillators. He has contrived an electronic analogue which imitates the vagaries of the A-V node during acute rheumatic fever, and he explains the synchronism that sometimes occurs in these terms: "When two oscillators of different rates are coupled, they tend to 'pull in'; that is, the less stable oscillator adopts the rate of the more stable oscillator or some harmonic of it. Physicists have long recognized this as a basic property of electrical oscillators and it proves to be a property of heart rhythmicity as well."

In conclusion, therefore, there can be little reasonable doubt that synchronization occurs, though it has not received general acceptance or recognition. By those who are acquainted with it the phenomenon is regarded as rare. We believe that it is probably not uncommon and that long leads combined with an awareness of the phenomenon will lead to its rather frequent recognition. Among the last sixteen examples of A-V dissociation seen by one of us, no less than seven (including the five presented herein) were considered to show probable or possible synchronization. The mechanism remains in doubt, although there are cogent reasons for believing that either mechanical or electrical influences can mediate it.

SUMMARY

1. During A-V dissociation there is a tendency for atria and ventricles to contract synchronously or almost synchronously.

2. Five examples of A-V dissociation manifesting this tendency to synchronize are presented.

3. Graded criteria for suspecting the presence of synchronization are suggested.

4. Possible mechanisms of A-V synchronization are briefly discussed.

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The Effect of Salicylates upon the Ventilatory Response to Carbon Dioxide in Patients with Pulmonary Emphysema and Hypercapnia*

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THE depressed ventilatory response to inhaled carbon dioxide in patients with pulmonary emphysema and carbon dioxide retention has been well documented [1-5]. The present study was designed to determine whether or not this abnormal response could be modified by the administration of salicylate or salicylate plus diamox. The effect of the administration of salicylate upon the respiratory depression following inhalation of high oxygen mixtures in patients with hypercapnia [6-7] was also investigated.

SUBJECTS

Ten male patients with obstructive pulmonary emphysema complicated by arterial oxygen unsaturation and carbon dioxide retention were studied. The vital statistics are given in Table 1. The diagnostic criteria were those that have been previously established for pulmonary emphysema [8].

As in a previous investigation [4], these patients were studied while their clinical status remained static; subjects with overt or suspected acute or recent pulmonary infections were specifically excluded. Previous episodes of right-sided heart failure had occurred in all subjects. Therapy therefore included digitalis, a low salt diet, intermittent mercurial injections and inhalation of bronchodilator aerosols. In contrast to individuals with heart disease of other etiologies [9], these men were able to tolerate a concentration of 5 per cent carbon dioxide in inspired air without difficulty.

METHODS

All subjects were studied in the basal postabsorptive state without prior sedation. The initial plan was to make four series of observations in each patient. During the first or control study (group 1), measurements of minute ventilation, arterial oxygen saturation, arterial carbon dioxide tension, arterial blood pH, oxygen consumption, carbon dioxide production,

respiratory quotient and respiratory rate were to be made while breathing compressed air, 3 per cent carbon dioxide in air, 5 per cent carbon dioxide in air, 5 per cent carbon dioxide in 95 per cent oxygen and 100 per cent oxygen.

The second set of studies (group 2) were planned after the acute administration of bufferin,† 1.8 gm. of acetylsalicylic acid at 6 P.M. and 0.6 gm. at 10 P.M., the night before the study, as well as 1.8 gm. at 8 A.M. the morning of the study.

The third set of studies (group 3) were to be performed after protracted administration of bufferin, 1.8 gm. three times a day for seven days.

The fourth set of studies (group 4) were planned after seven additional days of protracted administration of bufferin; during these latter seven days diamox® (500 mg. daily) was also given. All physiologic observations were to be repeated during the course of the latter three sets of studies. Four sets of observations were made in six patients. In four subjects all four sets of studies could not be obtained, as demonstrated in Tables I and II.

The detailed protocol of any one experiment is as follows. Duplicate measurements of the various physiologic variables were made while the inspired gas mixture consisted of compressed air. After a twenty minute rest period repeat observations were made while the subject was breathing 3 per cent carbon dioxide in air; after a second twenty minute rest period 5 per cent carbon dioxide in air was inhaled and repeat observations made. After another twenty minutes, 5 per cent carbon dioxide in 95 per cent oxygen was inhaled. A thirty minute rest period was then permitted the patient after which 100 per cent oxygen was administered. Measurements of only minute ventilation, arterial blood oxygen saturation, pH, and carbon dioxide tension were made during inhalation of the latter two gas mixtures.

All gas mixtures were breathed for at least fifteen

† Acetylsalicylic acid with magnesium carbonate and aluminum glycinate, Bristol Myers Co.

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TABLE 1 (Continued)
EFFECT OF DRUG THERAPY UPON THE VENTILATORY RESPONSE TO CO₂ IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA AND CO₂ RETENTION

Sub- ject	Age (yr.)	Sex	B. S. A.	% Predicted M. B. C.	Serum Salicylate (mg. %)	Breathing Mixture											
						Ambient Air				3% CO ₂ in Air				5% CO ₂ in Air			
						\dot{V}_E (L./min.)	f (per min.)	V_T (ml.)	\dot{V}_A (L./min.)	\dot{V}_E (L./min.)	f (per min.)	V_T (ml.)	\dot{V}_A (L./min.)	\dot{V}_E (L./min.)	f (per min.)	V_T (ml.)	\dot{V}_A (L./min.)
T. C.	46	M	2.00	14	0	6.97	16	373	2.74	7.98	18	443	3.04	10.1	19	531	3.42
1.					22.8	9.28	17.5	530	3.00	7.68	17.5	439	2.89	10.2	18.5	552	3.64
2.					22.3	7.83	16	489	2.80	8.04	19.5	412	3.20	10.3	17.5	588	3.55
3.					14.5	9.87	17	580	3.05	9.54	17	561	3.71	11.2	17.5	640	3.40
D. D.	68	M	1.87	29	0	7.94	20	397	3.18	11.0	22.5	489	4.75	15.0	24	625	6.14
1.					18.1	9.24	22	420	3.50	13.6	23	592	5.52	16.0	21	762	6.60
2.					16.5	8.45	19.5	434	3.10	11.2	21.5	521	4.56	14.8	21.5	689	5.53
3.					15.8	9.36	22	425	3.25	11.1	22.5	493	4.21	17.7	23	768	7.15
4.																	

Note: \dot{V}_E = minute ventilation in L./minute.
f = frequency of respiration per minute.
 V_T = tidal volume in cc. per breath.

\dot{V}_A = alveolar ventilation in L./minute.
B. S. A. = body surface area.
M. B. C. = maximum breathing capacity.

minutes (employing an open circuit) before the collection of either blood or expired gas samples was begun. The purpose of this time schedule was to permit attainment and maintenance of a "steady state" of respiration and circulation [10].

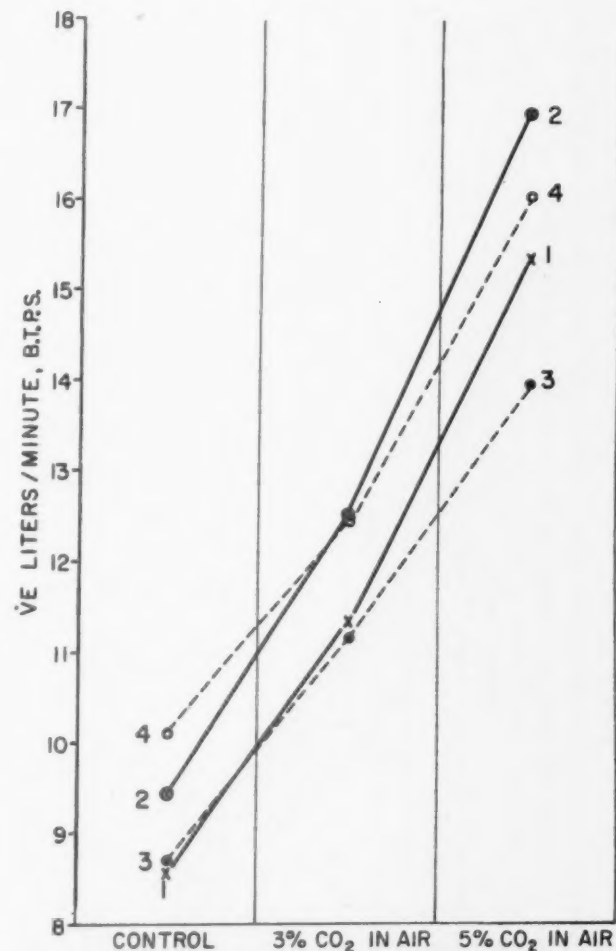


FIG. 1. Minute ventilation during inhalation of air, 3 per cent carbon dioxide in air, and 5 per cent carbon dioxide in air. Group 1 refers to the control data, group 2 to the acute salicylate study, group 3 to the chronic salicylate study and group 4 to the chronic salicylate plus diamox results. There is no significant difference in the slope of the four lines.

Expired gas samples were collected in a 120 L. Tissot spirometer and analyzed in duplicate for oxygen and carbon dioxide on a micro-Scholander apparatus, thus permitting calculation of oxygen consumption, carbon dioxide production, respiratory quotient and minute ventilation. Arterial blood was obtained via an indwelling Cournand needle and analyzed for oxygen and carbon dioxide content and for oxygen capacity on a Van Slyke apparatus. Arterial blood pH was determined at a constant temperature of 37°C. employing a Cambridge Research Model pH meter. The line charts of Van Slyke and

TABLE II (Continued)
EFFECT OF DRUG THERAPY ON GAS EXCHANGE AND ARTERIAL BLOOD COMPOSITION WHILE BREATHING COMPRESSED AIR, OXYGEN AND CO₂ MIXTURES
IN PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA AND CO₂ RETENTION

Sub- ject	Breathing Mixture																						
	Ambient Air					3% CO ₂ in Air					5% CO ₂ in Air					5% CO ₂ in 95% O ₂							
	Gas Exchange		Arterial Blood			Gas Exchange		Arterial Blood			Gas exchange		Arterial Blood			Arterial Blood		Arterial Blood					
	VO ₂ (L./min./M ²)	R	O ₂ Sat.	PaCO ₂ (mm. Hg)	pH	VO ₂ (L./min./M ²)	R	O ₂ Sat.	PaCO ₂ (mm. Hg)	pH	VO ₂ (L./min./M ²)	R	O ₂ Sat.	PaCO ₂ (mm. Hg)	pH	O ₂ Sat.	PaCO ₂ (mm. Hg)	pH	O ₂ Sat.	PaCO ₂ (mm. Hg)	pH		
T. C.																							
1.	119	.88	87	66	7.33	126	.75	92	76	7.28	126	.72	94	84	7.24	100	100	93	7.22	100	100	74	7.30
2.	133	.89	86	68	7.32	131	.75	93	79	7.27	141	.75	95	88	7.24	100	100	93	7.22	100	100	77	7.26
3.	133	.86	86	71	7.30	134	.75	93	77	7.27	155	.66	95	90	7.23	100	100	114	7.18	100	100	86	7.21
4.	132	.84	90	62	7.27	162	.60	92	68	7.24	149	.46	96	74	7.21	100	100	76	7.20	100	100	67	7.24
D. D.																							
1.	126	.80	87	52	7.39	165	.61	92	55	7.36	149	.66	95	64	7.31	100	100	68	7.28	100	100	61	7.33
2.	131	.85	88	53	7.40	185	.68	92	59	7.34	133	.77	95	63	7.31	100	100	67	7.29	100	100	58	7.34
3.	117	.83	87	51	7.40	161	.60	95	56	7.35	134	.60	96	62	7.31	100	100	69	7.27	100	100	61	7.30
4.	131	.81	89	55	7.27	157	.63	96	61	7.22	151	.64	97	67	7.19	100	100	70	7.18	100	100	65	7.20

Sendroy permitted calculation of arterial blood carbon dioxide tension.

Alveolar ventilation was calculated from the minute volume, arterial blood carbon dioxide tension, respiratory rate and the expired gas carbon dioxide tension.

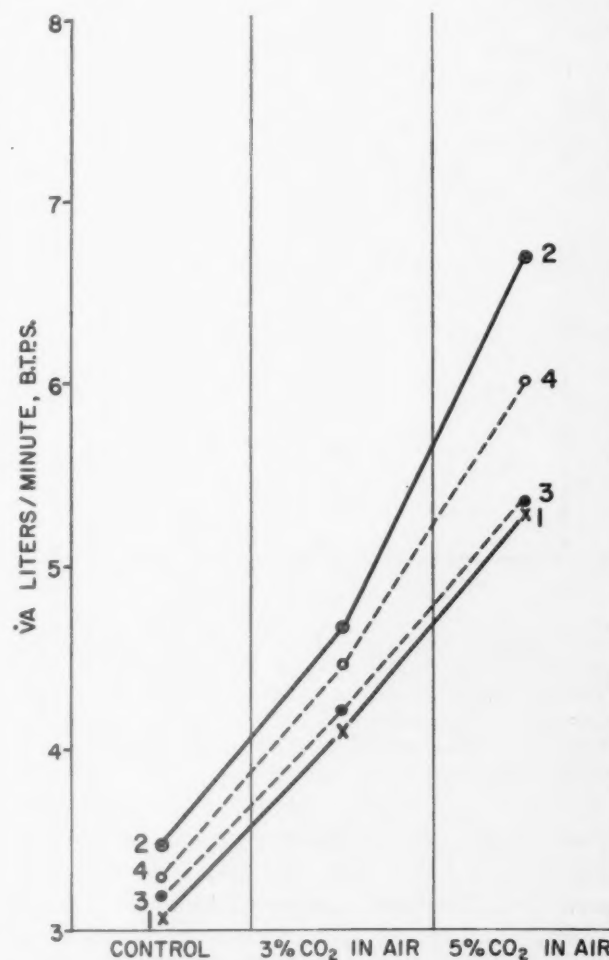


FIG. 2. Alveolar ventilation data obtained under the same conditions as in Figure 1. There is again no significant difference in the slope of the four lines.

Serum salicylate levels were determined by the method of Brodie, Udenfriend and Coburn [17].

RESULTS

The effects of the administration of salicylate or salicylate plus diamox upon the ventilatory responses to carbon dioxide inhalation and upon gas exchange during such inhalation are summarized in Tables I and II. The average increases in minute ventilation ($\dot{V}E$) and alveolar ventilation ($\dot{V}A$) during the four groups of studies are illustrated in Table III. The control increase in minute ventilation on 5 per cent carbon dioxide is 77 per cent; this is similar to the 58 per

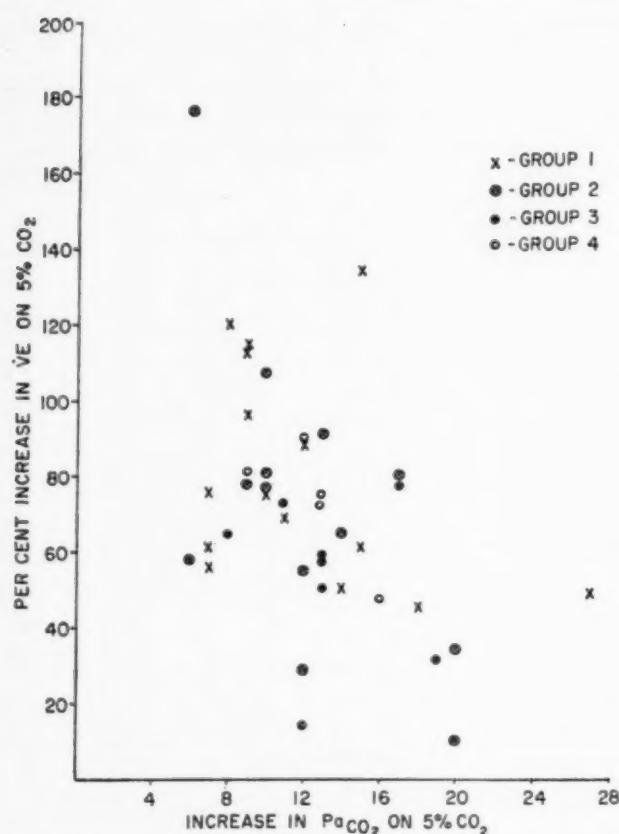


FIG. 3. Scatter diagram of the relationship between the per cent increase in \dot{V}_E and the increase in PaCO_2 on 5 per cent carbon dioxide as compared to room air. There is no relation between the rise in \dot{V}_E and the increment in PaCO_2 , either during control conditions or during salicylate therapy.

cent increase noted during a previous study [4] and is well below the 187 per cent increase noted in a control group of eleven hospital "normal" subjects during this earlier study. The administration of salicylate with or without diamox did not effect any increase in the ventilatory response to carbon dioxide, measured as the per cent increase in \dot{V}_E or \dot{V}_A . There is also little effect upon the respiratory rate under these conditions. (Table IV.)

TABLE III
EFFECT OF SALICYLATE ADMINISTRATION UPON THE VENTILATORY RESPONSE TO 5 PER CENT CO_2

Group	% Increase \dot{V}_E (air—5% CO_2)	% Increase \dot{V}_A (air—5% CO_2)
1	77	75
2	75	87
3	59	64
4	59	84

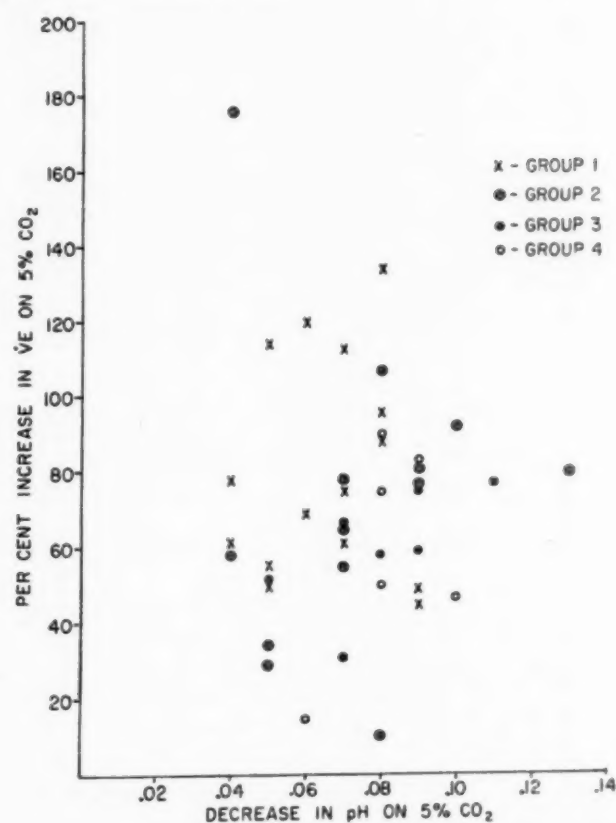


FIG. 4. Scatter diagram of the increments in \dot{V}_E and decrements in pH on 5 per cent carbon dioxide. Salicylate administration has not increased the ventilatory response to a fall in arterial blood pH.

The same data are illustrated in Figures 1 and 2. The numbers 1, 2, 3 and 4 refer to the four groups described under Methods. The slope of the increase in minute or alveolar ventilation is the same under control conditions (group 1), under acute salicylate administration (group 2), under protracted salicylate administration (group 3), or under protracted salicylate and diamox administration (group 4). These results suggest that the sensitivity of the respiratory center to carbon dioxide is not increased by salicylate therapy. Salicylate serum levels varied

TABLE IV
EFFECT OF SALICYLATE ADMINISTRATION UPON THE RESPIRATORY RATE DURING THE INHALATION OF VARIOUS GAS MIXTURES

Group	Compressed Air	3% CO_2	5% CO_2
1	21.6	22.5	24.7
2	21.8	21.9	23.2
3	20.4	22.1	22.4
4	22.1	22.5	22.8

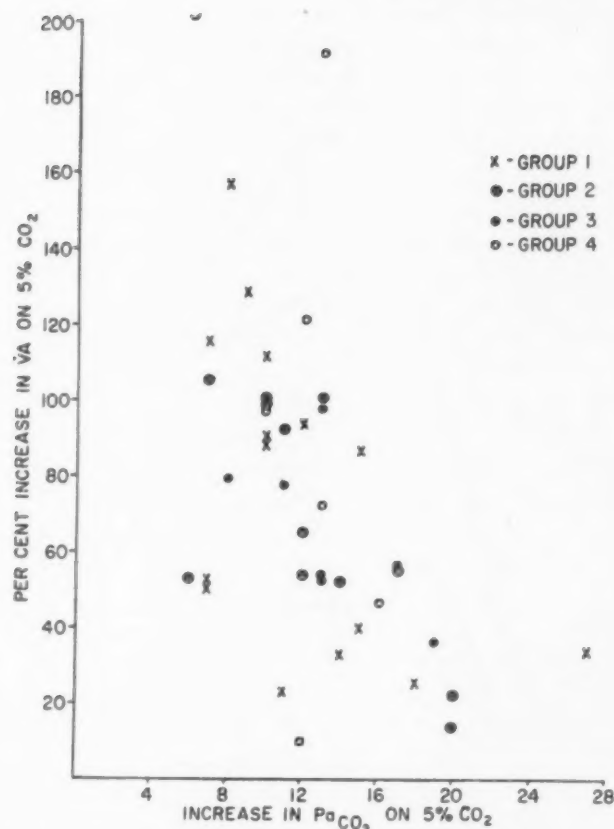


FIG. 5. Scatter diagram of the increments in \dot{V}_A and PaCO_2 during inhalation of 5 per cent carbon dioxide.

from 11 to 30 mg. per cent during these investigations. Figures 1 and 2 also demonstrate that both minute and alveolar ventilation usually increase somewhat when salicylates are given, both under control conditions and when 3 per cent and 5 per cent dioxide are inhaled.

Figures 3 to 6 reveal in another manner that the sensitivity of the respiratory center to carbon dioxide is not increased by salicylate treatment. There is no relation between the increase in \dot{V}_E

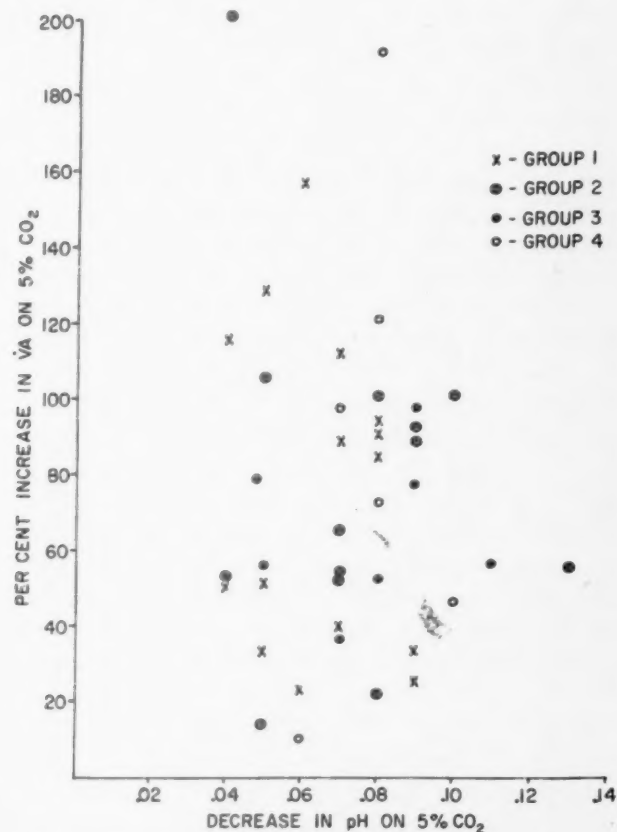


FIG. 6. Scatter diagram of the increase in \dot{V}_A and the decrease in pH on 5 per cent carbon dioxide. The relationships are unchanged by salicylate administration.

or \dot{V}_A and the increase in arterial carbon dioxide tension (PaCO_2) or the decrease in arterial blood pH (during 5 per cent carbon dioxide inhalation) either under control conditions or during salicylate therapy.

The effect of salicylate administration upon gas exchange and arterial blood composition while on room air is shown in Table v. There is no change in arterial oxygen saturation or in

TABLE V
EFFECT OF SALICYLATE ADMINISTRATION UPON GAS EXCHANGE AND ARTERIAL BLOOD COMPOSITION WHILE BREATHING ROOM AIR

Group	Arterial O_2 Saturation		PaCO_2 (mm. Hg)		$\dot{V}\text{O}_2$ (ml./min./ M^2)		R		pH	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
1	84	(71-94)	59	(47-76)	129	(112-161)	.85	(.79-.93)	7.36	(7.33-7.40)
2	84	(79-95)	58	(39-68)	140	(123-170)	.85	(.82-.94)	7.36	(7.32-7.40)
3	85	(71-90)	57	(50-75)	140	(123-169)	.87	(.83-.93)	7.35	(7.30-7.40)
4	88	(85-91)	57	(54-65)	139	(131-159)	.83	(.72-.90)	7.28	(7.24-7.33)

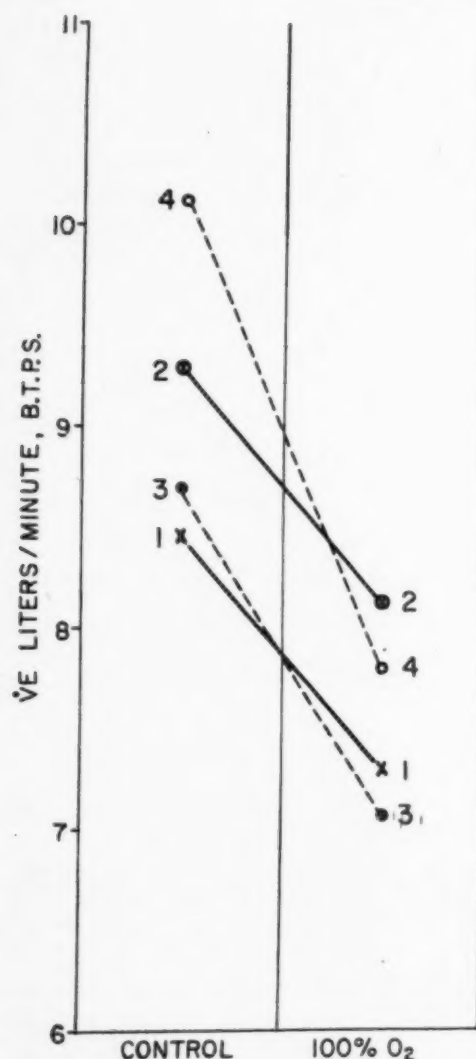


FIG. 7. Effect of inhalation of oxygen-rich gas mixtures upon \dot{V}_E under the various conditions previously discussed. Salicylates do not inhibit the fall in \dot{V}_E .

arterial carbon dioxide tension. Arterial blood pH is also unchanged except for the decrease occasioned by diamox. The respiratory quotient shows little variation under drug treatment; on

TABLE VI
EFFECT OF SALICYLATE ADMINISTRATION UPON PaCO_2
DURING INHALATION OF O_2 RICH GAS MIXTURES

Group	Increase PaCO_2	
	Air— O_2	5% CO_2 in Air—5% CO_2 in 95% O_2
1	9	9
2	8	6
3	9	11
4	8	6

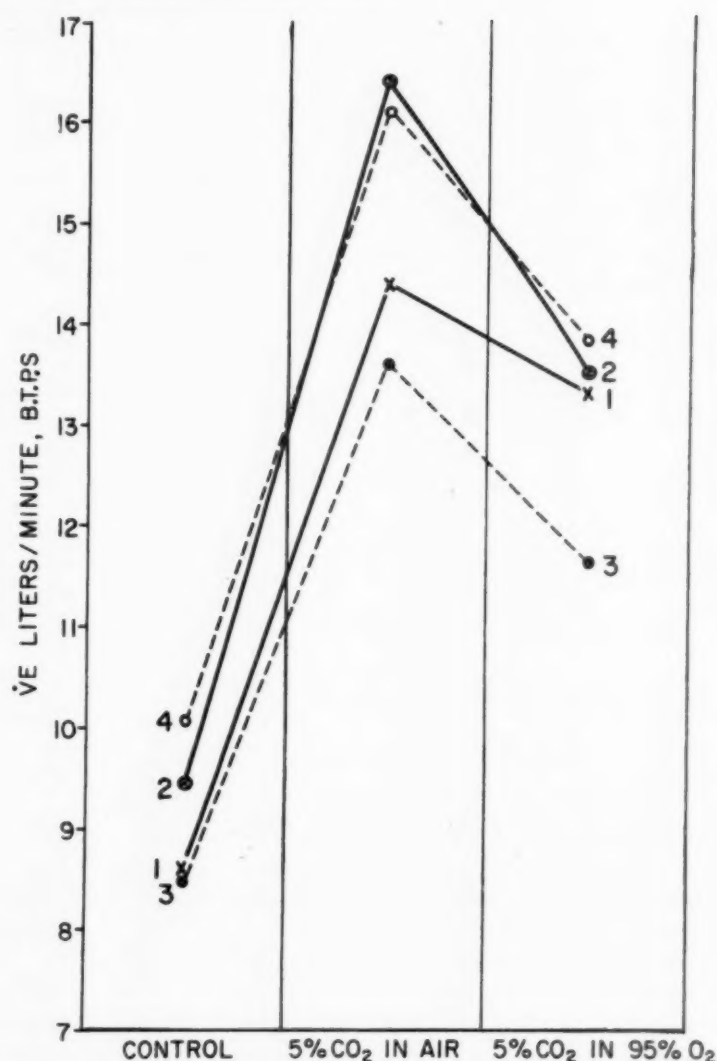


FIG. 8. Effect of inhalation of oxygen-rich gas mixtures upon the ventilatory response to 5 per cent carbon dioxide. The depressant effect of 95 per cent O_2 is not reversed by salicylate therapy.

the other hand there is a small but definite increase in oxygen consumption. Since the respiratory quotient is unchanged, carbon dioxide production increased proportionately to the increase in oxygen consumption. Since alveolar ventilation, carbon dioxide production and arterial carbon dioxide tension are interrelated,

$$\dot{V}_A = \frac{\dot{V}\text{CO}_2}{\text{PaCO}_2} \div (B - 47)$$

(where B =
the atmospheric pressure in mm. Hg)

the increase in $\dot{V}\text{CO}_2$, with an unchanged PaCO_2 during salicylate administration, must

result in an increase in \dot{V}_A . As noted, an increase in \dot{V}_A was found during bufferin therapy.

The effect of salicylate therapy upon the respiratory depression following inhalation of oxygen rich mixtures is illustrated in Table VI and in Figures 7 and 8. Table VI demonstrates that salicylate administration has no effect upon the increase in P_{aCO_2} when a change from inhalation of compressed air to inhalation of 100 per cent oxygen is made; the same is true when a change is made from 5 per cent carbon dioxide in room air to 5 per cent carbon dioxide in 95 per cent oxygen. Figures 7 and 8 illustrate that the decrease in ventilation following inhalation of oxygen rich gas mixtures is not prevented by salicylate or by salicylate plus diamox treatment.

COMMENTS

Previous investigators [12,13] have suggested that salicylates produce an increase in the sensitivity of the respiratory center to the normal chemical stimuli affecting this structure. Alexander *et al.* [12] noted a greater ventilatory response to inhaled carbon dioxide in three normal subjects after salicylate administration. In view of the depressed sensitivity of the respiratory center to inhaled carbon dioxide in patients with obstructive pulmonary emphysema and hypercarbia [4], the present study was undertaken in an attempt to find a means of reducing the degree of carbon dioxide retention frequently found in obstructive pulmonary emphysema.

Wegria *et al.* [14] found that oral salicylate administration (with plasma salicylate levels of 10 to 35 mg. per cent) was successful on occasion in reducing the degree of hypercapnia in pulmonary emphysema. Similar serum salicylate levels were achieved in the present study, but no change was demonstrable in arterial oxygen saturation, arterial carbon dioxide tension, arterial blood pH, respiratory quotient, or in the ventilatory response curve to inhaled carbon dioxide. (Table III, Figs. 1 and 2.) Control levels of ventilation were increased (while breathing room air) after salicylate therapy compared to pre-salicylate levels. The same increase in ventilation was noted when \dot{V}_E values breathing 3 per cent carbon dioxide and 5 per cent carbon dioxide in air were compared before and after salicylate administration. However, the per cent increases in \dot{V}_E and \dot{V}_A on 3 per cent and 5 per cent carbon dioxide (compared

to control room air values) were not increased on salicylate treatment. That is, the slope of the ventilatory response curve during carbon dioxide inhalation was not increased during salicylate therapy. (Table III, Figs. 1 and 2.)

The increase in ventilation is secondary to the metabolic effect of salicylates. As seen in Table V, salicylate administration produced an increase in oxygen consumption. Similar metabolic effects have been noted by other investigators [15,16].

Wegria *et al.* [14] noted that salicylates were occasionally effective in reducing the degree of added carbon dioxide retention developing after oxygen administration in patients with hypercapnia. Such an effect was not found in the present study. (Table VI, Figs. 7 and 8.) The inability of salicylate therapy to prevent further carbon dioxide retention in patients with hypercarbia who are exposed to oxygen rich gas mixtures is disappointing and removes a potentially valuable weapon from our therapeutic armamentarium.

The depressed ventilatory response to inhaled carbon dioxide in emphysema with carbon dioxide retention is apparently not reversible by salicylates. To date reversal of this abnormal response in pulmonary emphysema has rarely been found. Boutourline-Young and Whittenberger [17] presented data suggesting such a change in 1951. Burwell *et al.* [18] have recently published a case report demonstrating a return of respiratory center sensitivity to inhaled carbon dioxide after considerable weight loss in an obese subject with alveolar hypoventilation. Neither of these two latter patients received salicylates. Cherniack and Snidal [19] have reported partial reversal of the depressed ventilatory response to inhaled carbon dioxide in emphysematous subjects by means of bronchodilator therapy. Interpretation of these latter results is hampered by the absence of gas exchange and arterial blood gas tension data in these patients.

SUMMARY

Oral acute and prolonged salicylate administration to ten male patients with obstructive pulmonary emphysema and hypercarbia failed to improve the impaired ventilatory response to inhaled carbon dioxide so characteristic of this group of subjects. Ventilatory depression consequent to inhalation of high oxygen gas mixtures was not inhibited, in these patients, by salicylate therapy.

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Some Effects of Change in Position on Pulmonary Function in Bronchial Asthma*

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PATIENTS with bronchial asthma often describe an increase in severity of symptoms after retiring at night. This symptomatic increase in asthma is variable, as is the time of onset after assuming the recumbent position. The phenomenon has been ascribed most often to changes in the volume of various lung compartments, exposure to allergens or to relaxation in sleep and the attendant physiologic changes.

We have studied the role that a shift from the erect to the supine position may play by measuring changes in the compartmental volume and rate of airflow during a maximal expiratory effort in a group of asthmatic patients and in normal healthy control subjects.

METHODS

Twenty-six asthmatic subjects varying in age from eighteen to sixty-five years and thirteen normal control subjects varying in age from twenty-one to fifty-five years were studied. The asthmatic subjects included nine females and seventeen males. Seventeen of the twenty-six patients had had severe asthma for five or more years. The remaining nine patients had had mild to moderate asthma of two to three years' duration, all had highly reversible disease, and all were sensitive by skin test to one or more allergens. The normal subjects included seven females and three males, all of whom had no history or evidence of respiratory disease.

These subjects were tested at various intervals during a six-month period. The study was conducted in the following manner. Measurements were made with the subject in the erect and in the recumbent position, using a standard tilt-table. Respiration was recorded using a closed system previously described [1] and minute ventilation, vital capacity, total lung capacity, expiratory reserve volume, functional residual capacity and residual volume were obtained by the helium dilution method [2].

The measurements were first made with the subject in the erect position. The subject was then placed in the recumbent position for five to ten minutes and the

measurements were repeated. The asthmatic subjects were tested on more than one occasion and therefore at various stages of their illness.

RESULTS

The results of forty-one separate determinations in the twenty-six asthmatic patients and of thirteen determinations in the ten control subjects are shown in Table I.

The changes in vital capacity in both groups are shown graphically in Figure 1. Statistic analysis showed that upon assuming the recumbent position the decrease in vital capacity in the control group was significantly greater ($p = <.035$) than in the asthmatic group.

In addition, the volume expired during the first second in both the asthmatic group and in the normal control group was studied and compared. No significant change occurred in either group upon assuming the recumbent position.

COMMENTS

This study was largely limited to the static changes in pulmonary function which occur in changing from the erect to the supine position. It was anticipated that when this shift was made a fall in vital capacity would occur, superimposed on an already decreased vital capacity, and that this would explain the almost universal complaint among asthmatic patients that they become worse during the sleeping hours. As seen graphically in Figure 1, not only was the decrease in vital capacity not seen as frequently as had been anticipated, but an increase occurred in a significant number of patients, for the most part in those who were sickest.

It has been known for over 100 years that the vital capacity decreases in the normal subject when the recumbent position is assumed [3]. Hamilton and others have demonstrated that the greater portion of the decrease in vital capacity

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ity can be explained by the increased pulmonary blood volume attending the supine position [4]. This decrease in vital capacity can be modified by the application of pressure cuffs on the extremities to prevent return of venous blood to the thoracic cavity [5]. McMichael and

TABLE I
CHANGES IN THE COMPARTMENTAL LUNG VOLUMES UPON
TILTING TO THE HORIZONTAL POSITION

Direction of Change*	Patients		Normal Subjects	
	No.	%	No.	%
<i>Vital Capacity</i>				
Decrease.....	21	52	11	85
Increase.....	10	24	0	0
No change...	10	24	2	15
<i>Total Lung Capacity</i>				
Decrease.....	29	71	9	69
Increase.....	9	22	4	31
No change...	3	7	0	0
<i>Expiratory Reserve Volume</i>				
Decrease.....	27	66	13	100
Increase.....	11	27	0	0
No change...	3	7	0	0
<i>Functional Residual Capacity</i>				
Decrease.....	32	78	9	70
Increase.....	9	22	2	15
No change...	0	0	2	15
<i>Residual Volume</i>				
Decrease.....	23	56	8	62
Increase.....	13	32	3	23
No change...	5	12	2	15

* >100 ml.

McGibbon, continuing the earlier studies by Hurtado and Fray [6,7], studied patients in both the erect and supine positions and found that the total lung volume, functional residual capacity, vital capacity and residual volume decreased during recumbency. Not only do the abdominal contents push the diaphragm cephalad, with concomitant pooling of blood in the lesser cir-

culatation, but the recumbent position may place the muscles of respiration at a disadvantage. Among the factors mentioned, the cephalad shift of the diaphragm with its effects on the subdivisions of the pulmonary volume has received most attention, and the changes observed in this study are presumably a reflection of this shift, perhaps combined with the shift in blood into the thoracic cage.

Some studies in chronic obstructive pulmonary emphysema, a disease exhibiting many of the features of asthma, indicate that the cephalad shift of the diaphragm induced by pneumoperitoneum is beneficial [8]. This conclusion should be tempered, however, by the statement of many patients with emphysema that abdominal compression aggravates symptoms. This is not surprising when it is recalled that the lowered diaphragm in emphysema is a consequence, not the cause, of the pulmonary lesion, characterized as it is by obstruction to air flow readily demonstrable with even the crudest measurements. In emphysema, resistance to flow in the airway increases as the lung diminishes in volume and indeed this may be regarded as a gross exaggeration of similar changes which take place in the normal subject. Thus, any measure which would result in compression of the lung would be expected to aggravate the functional defect and indeed this is borne out by our own clinical experience. In adopting a position of inspiration, with its associated increased patency of the airway, the patient with obstructive pulmonary disease suffers less from the consequences of a narrowed airway and in this sense the inspiratory position and lowered diaphragm are an adjustment to the disease process. Eating a large meal, bending forward to tie a shoe or wearing a tight belt have been aggravating factors in our patients with any form of severe diffuse bronchial obstruction. We believe, therefore, that it is premature at this time to assume that the benefits attributed to pneumoperitoneum in emphysema are necessarily a result of the upward shift of the diaphragm, a shift which presumably occurs in some degree in any person, when changed from the erect to the supine position.

Bronchial asthma exhibits the same changes as emphysema with the difference that the vital capacity tends to be decreased roughly in proportion to the severity of symptoms and the disease process is usually entirely or to a large degree reversible. Other factors such as a change

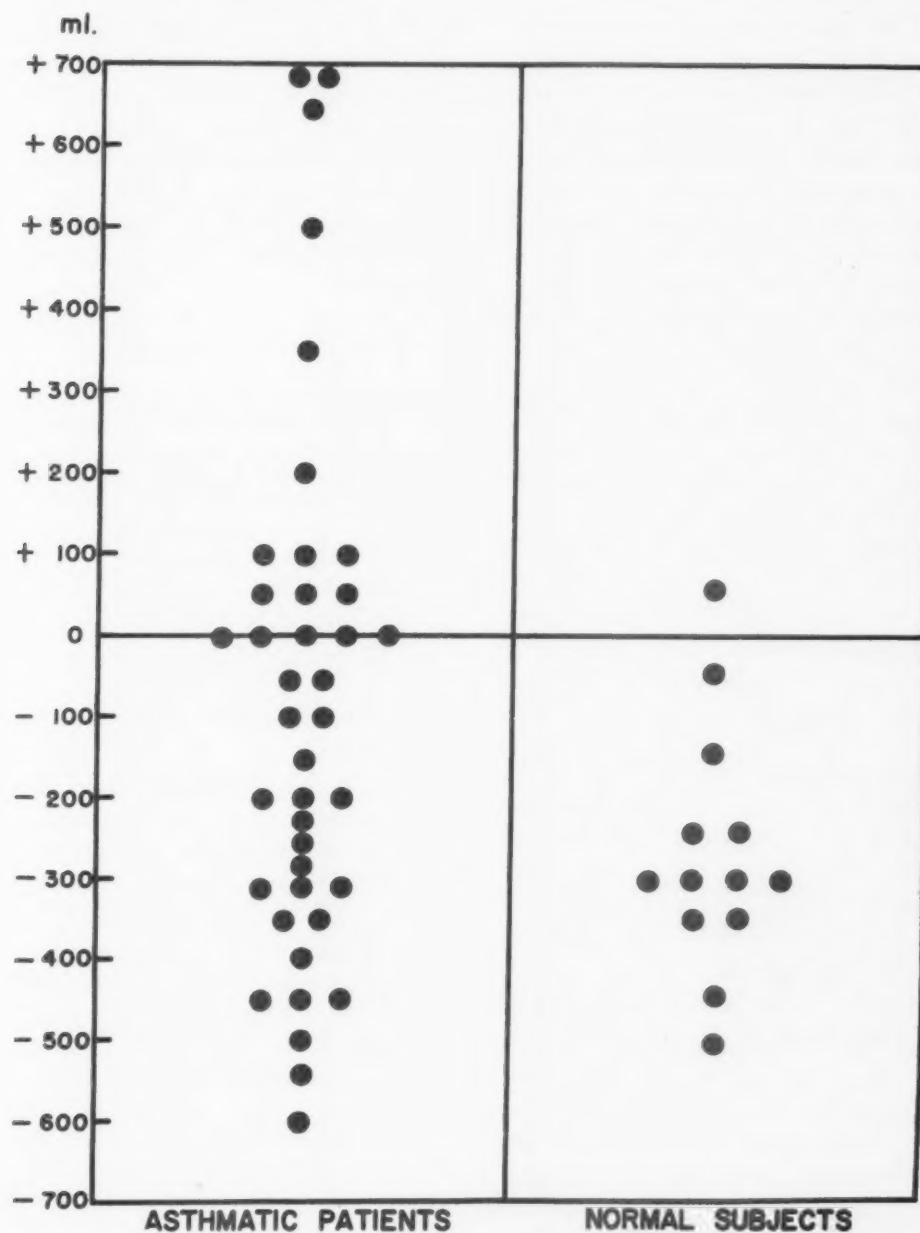


FIG. 1. Change in vital capacity upon tilting to the horizontal position.

in the intrapulmonary distribution of the inspired air, local changes in blood flow, or changes in compliance and mechanical resistance within the lung [9] may play a part when the subject's position is shifted, changes which would not be revealed by the studies carried out here or by those which have been made in the past. In addition, it has been the common clinical experience that, in contradistinction to patients with obstructive emphysema, those with bronchial asthma seem to have increased symptoms upon lying down.

Certain considerations may explain the clinical impression that, for a given degree of respira-

tory obstruction, the patient with asthma will be far more dyspneic than the patient with emphysema, and one would therefore expect that orthopnea, a response to dyspnea, would likewise be more common in the asthmatic subject. This difference may be explained in part at least by the relatively frequent occurrence of respiratory acidosis in emphysema on the one hand and its infrequency in asthma. Not only will a lower level of ventilation than would otherwise be necessary suffice for the excretion of CO_2 in the presence of respiratory acidosis, but the consequent decrease in respiratory work upon assuming the recumbent position will lessen

the amount of CO_2 which must be disposed of. Furthermore, as there appears to be an associated decrease in the respiratory responsiveness to CO_2 , a rise in CO_2 accompanying aggravation of obstruction would be accompanied by less dyspnea in the presence of respiratory acidosis than in its absence. The asthmatic subject with a paroxysmal illness will not allow this "adaptation" to occur and therefore drives his respiratory muscles to achieve the excretion of CO_2 . In so doing he increases the amount of CO_2 to be excreted and thereby establishes a vicious circle. We are not aware that these factors have been studied in relation to postural effects. It would be premature at this time to assume that the clinically recognized differences in the two conditions are a consequence of a difference in the nature of the respiratory difficulty other than that pertaining to the magnitude of the respiratory defect and its persistence.

SUMMARY

1. The compartmental lung volumes in twenty-six asthmatic patients and in ten normal subjects were studied in an effort to determine whether or not the change from the erect to the supine position could explain the increase in respiratory symptoms which so commonly occurs at night in bronchial asthma.

2. The predominant change in both groups was a fall in the vital capacity upon assuming the

horizontal position. However, the vital capacity increased in one-third of the patients with asthma whereas no such increase was observed among the normal subjects.

3. Factors other than an immediate change in the vital capacity and compartmental lung volumes must play a role in the genesis of a nocturnal increase in symptoms in asthmatic patients.

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Hypercalcemic Crisis Due to Hyperparathyroidism*

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KNOWLEDGE of the clinical features of hyperparathyroidism has developed through recognition that this disease may involve multiple body systems and thus be manifested by a variety of symptom complexes. In the diagnosis of the first detected cases emphasis was placed on the evidence of generalized bone disease, osteitis fibrosa cystica [1-4]. Soon thereafter it was recognized that renal dysfunction with polyuria, azotemia and/or renal calculi often occurred in patients with hyperparathyroidism [5-7]. Indeed, in most cases the diagnosis of hyperparathyroidism was first suspected because of the presence of renal calculi or nephrocalcinosis [8]. Although it was pointed out early that there were patients in whom gastrointestinal symptoms were predominant [9-11], some years elapsed before the frequency of nausea, vomiting and abdominal pain (with or without demonstrable peptic ulcers) was generally appreciated [12-14].

Another distinct group of manifestations which may occur in hyperparathyroidism was first reported in man by Lowenborg and Ginsburg [15]. In a boy with purpura hemorrhagica, to whom they had given parathyroid hormone in doses much larger than intended, nausea and vomiting developed within two days; he then became weak, lethargic and unresponsive to noxious stimuli. At this time the concentration of serum calcium was 19.6 mg. per cent and phosphorus 4.4 mg. per cent. Cessation of parathyroid hormone administration was followed by a return to normocalcemia and prompt disappearance of nausea, vomiting, and stupor. Subsequently, a number of patients with hyperparathyroidism have been reported in whom this symptom complex of intractable nausea and

vomiting, progressive drowsiness and coma developed. These symptoms usually developed in association with a high serum calcium concentration and were preceded or accompanied by decreasing urine volume, a rising serum phosphorus,† and progressive azotemia [16-32]. A brief resume of the previously reported patients with hyperparathyroidism manifesting this clinical syndrome is given in Table 1. Many of these patients died within a few days after onset of symptoms, the correct diagnosis being established by postmortem examination. However, in a number of cases [25-32] prompt recognition and treatment averted a potentially fatal course. Failure to recognize the clinical state induced by marked hypercalcemia may partially account for the scarcity of successfully treated cases.

Three patients with hyperparathyroidism who presented with this syndrome have been seen recently. In two, an emergency removal of a parathyroid adenoma resulted in a successful outcome. In the third patient the correct diagnosis was suspected only two hours before death.

CASE REPORTS

CASE 1. E. F. (J. H. H. No. 722087), a sixty-nine-year-old woman, was admitted to the medical wards on November 11, 1955, with a history of having had for four days recurrent, severe anterior chest pain which radiated into both shoulders and down the left arm. She had had hypertension for several years and gave a history of recurrent, bilateral renal calculi for five years, during which time she had been subjected to nephrolithotomy on three different occasions. The patient had been aware of a tumor in her neck

† The term "serum phosphorus" is used throughout this paper to refer to the inorganic phosphorus of the serum.

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TABLE 1
FATAL AND NON-FATAL CASES OF HYPERPARATHYROIDISM EXHIBITING THE SYNDROME
ASSOCIATED WITH MARKED HYPERCALCEMIA *

Authors	Predominant Symptoms	Serum		Azotemia
		Calcium (mg./100 ml.)	Inorganic Phosphorus (mg./100 ml.)	
Fatal Cases				
Hanes [16].....	Weak, emotionally depressed, apprehensive	20	4.7	Present
Oliver [17]. Case I.....	Nausea, vomiting, drowsiness, weakness	17 (postmortem)	Unknown	Present
Case II.....	Nausea, vomiting, drowsiness, weakness	20 (postmortem)	Unknown	Present
Smith and Cooke [18].....	Abdominal pain, nausea, vomiting, lethargy, disoriented	23	4.8	Present
Mellgren [19].....	Abdominal pain, nausea, vomiting, apathetic, weak	Unknown	Unknown	Present
McClure and Lam [20].....	Nausea, vomiting, mental confusion	14 → 19	2.5 → 6.3	Unknown
Rogers [27]. Case I.....	Abdominal pain, vomiting, weakness, apathy, coma	Unknown	Unknown	Present
Case II.....	Abdominal pain, vomiting, lethargy, coma	Unknown	Unknown	Present
Young and Emerson [22]....	Nausea, vomiting, weakness	22	3.4	Present
Staub, Grayzel and Rosenblatt [23]	Abdominal discomfort, weakness, vomiting, apathy	14	2.1	Unknown
Anderson and McWhorter [24]	Nausea, vomiting, weakness	18	6.2	Present
Non-Fatal Cases				
Morelle [25].....	Epigastric pain, nausea, vomiting	18	1.4	Present
Schrumpf and Harbitz [26]...	Nausea, vomiting, weakness	21 → 18	1.2	Present
Fitz and Hallman [27].....	Thirsty, mental confusion, coma	16 → 19	2.2	Present
Schneider [28].....	Weakness, nausea, vomiting	29	2.1	Present
Howard, Folis, Yendt and Connor [29].....	Epigastric pain, nausea, vomiting	13 → 20	3.0 → 5.0	Present
James and Richards [30].....	Epigastric pain, nausea, stuporous	15 → 17	1.8	Present
Bradlow and Segal [37].....	Weakness, nausea, confused	21 → 13	2.7 → 3.2	Present
Harmon [32].....	Vomiting, lethargy, convulsions	12 → 19	1.8 → 3.6	Present

* Included in this table are those reported cases of hyperparathyroidism which seemed to most certainly portray the syndrome associated with marked hypercalcemia. Not included are other reported cases of fatal hyperparathyroidism [32-36] in which details of the clinical course were not given or other possible causes of death existed.

for four years. During the two years preceding admission she had been anorexic, weak and constipated, and had lost 55 pounds in weight.

On admission, examination revealed an elderly woman who was moderately obese, alert, cooperative and did not appear to be in acute distress. The blood pressure was 184/96 mm. Hg, respirations 18 per minute and temperature 98.6°F. A mass four to five times the size of a normal lobe of the thyroid was palpable superior and posterior to the left sternoclavicular joint. The heart was slightly enlarged,

and heart sounds were distant. The physical examination was otherwise unrevealing.

The laboratory data revealed the hematocrit to be 40 per cent, corrected sedimentation rate 38 mm. per hour, white blood cells 9,000 per cu. mm. Repeated urinalysis showed a persistent microscopic hematuria; phenolsulfonphthalein excretion was 15 per cent in two hours. An x-ray film of the abdomen revealed bilateral renal calculi. The pertinent chemical analyses of blood and urine obtained during hospitalization are recorded in Table II. The serum concentrations of

TABLE II
CHEMICAL DETERMINATIONS
CASE I, E. F.

Date	Serum					Urine		
	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (Bodansky units)	Non-protein Nitrogen (mg./100 ml.)	Total Protein (gm./100 ml.)	Volume (ml./24 hr.)	Calcium* (mg./24 hr.)	Phosphorus (mg./24 hr.)
11/12/55	14.4	2.2	5.4	35	...	1520	205	298
11/15/55	16.0	3.3	5.3	51	6.8	1550	170	506
11/19/55	18.1	3.9	...	55
11/22/55	18.3	3.8	...	60	...	760	230	...
11/25/55	18.2	3.6	...	63	...	2040	334	365
11/27/55	18.0	3.3	...	50
Operation 11/27/55								
11/28/55	15.8	3.1	...	55	6.8
11/30/55	12.5	3.1	4.2	68	...	830	113	48
12/ 2/55	10.9	3.0	...	74	...	2500	153	183
12/ 5/55	8.9	2.8	7.0	55	...	1920	46	149
12/13/55	9.0	3.9	5.3	57	7.1	2330	38	203

* Dietary calcium less than 300 mg. per twenty-four hours.

sodium, potassium, bicarbonate and chloride were normal.

The initial impression of a recent myocardial infarction was confirmed by serial electrocardiograms. Because of the presence of bilateral renal calculi, serum calcium and phosphorus determinations were obtained. These revealed a persistent hypercalcemia with hypophosphatemia. A roentgenologic survey of the skeleton showed no evidence of osteitis fibrosa except for suggestive subperiosteal bone resorption in several of the phalangeal bones of the hands. Thus, in addition to a myocardial infarction, it was believed that this patient had hyperparathyroidism.

The patient was kept at bed rest, and during the second week of hospitalization it was noted that she was becoming lethargic and anorexic. Also, the blood non-protein nitrogen and serum calcium and phosphorus concentrations were increased over the values obtained on admission. The daily urine volume had become much reduced. Augmenting the fluid intake increased the urine output, but did not ameliorate the symptoms. By the end of the second week of hospitalization the patient was quite drowsy, confused, nauseated, and had begun to vomit. It was considered that, despite the recent myocardial infarction, the danger from the steadily increasing hypercalcemia was greater than the operative risk, so immediate exploration for a parathyroid adenoma was advised. At operation, performed by Dr. Arthur R. Nelson, a 101 gm. parathyroid adenoma extending from beneath the left lobe of the thyroid down into the mediastinum was removed. The patient tolerated the operation well and experienced no cardiac complications.

Postoperatively there was a prompt change in symptoms with cessation of nausea and vomiting and disappearance of lethargy and mental confusion within twenty-four hours. The serum calcium concentration

was normal by the fifth day postoperatively, but the blood non-protein nitrogen continued to rise for some days after operation and, although decreasing, had not returned to normal by the time of discharge from the hospital.

Two months later the patient was readmitted for removal of a left ureteral calculus (shown by subsequent analysis to consist of calcium oxalate and phosphate). A staghorn calculus was present on the right, and there was no evidence of function of the right kidney by intravenous pyelography. The serum calcium and phosphorus concentrations were normal. The non-protein nitrogen was 34 mg. per cent, and phenolsulfonphthalein excretion was 30 per cent in two hours.

Comment: Hyperparathyroidism had undoubtedly existed in this patient for years. It is believed that immobilization incident to the myocardial infarction may have accentuated the hypercalcemia and thus induced the associated clinical manifestations. Active mobilization did not seem justifiable, and increasing the fluid intake was ineffective in altering the clinical state. Therefore, immediate operative intervention seemed imperative. The response following operation was gratifying, for it is not known at what stage the events associated with marked hypercalcemia might have become irreversible.

CASE II.* M. G. (J. H. H. No. 723404), a fifty-five year old retired machinist, was admitted to the hospital on November 28, 1955, complaining of pain in the legs and back of ten to fifteen years' durations

* The authors are indebted to Dr. John Collins Harvey for permission to study and report on this patient.

TABLE III
CHEMICAL DETERMINATIONS
CASES II AND III

Date	Serum					Urine		
	Calcium (mg./100 ml.)	Phosphorus (mg./100 ml.)	Alkaline Phosphatase (Bodansky units)	Non-protein Nitrogen (mg./100 ml.)	Total Protein (gm./100 ml.)	Volume (ml./24 hr.)	Calcium* (mg./24 hr.)	Phosphorus (mg./24 hr.)
<i>Case II, M. G.</i>								
11/29/55	15.7	37	7.1
12/ 1/55	16.2	1.4	5.2
12/ 3/55	16.2	2.5	5.7	38	...	1970	524
12/ 5/55	19.1	2.5	...	38	...	2030	596	1385
12/ 6/55	20.6	2.5	...	43	...	1550	564	1120
12/ 7/55	20.8	3.0
Operation 12/7/55								
12/ 8/55	16.9	3.2	...	56	...	870	175	246
12/10/55	13.2	2.6	4.9	80	...	1240	104	34
12/14/55	10.0	2.5	4.6	54	...	1380	72	24
<i>Case III, B. M.</i>								
1/16/56	4.3	4.1	44
1/20/56	88
1/23/56	17.3	174

* Dietary calcium less than 300 mg. per twenty-four hours.

For thirty years he had had "indigestion" characterized by nausea, gaseous eructations and burning epigastric pain for which he took up to six tablespoons of sodium bicarbonate daily in addition to "large amounts" of milk. These symptoms had increased in severity during the eight years before admission. For fifteen years he had complained of persistent low back pain and for ten years had noted intermittent pain without swelling in both knees. In 1954 (two years before admission) the patient experienced several episodes of left renal colic and passed one small calculus. He had also been aware of urinary frequency with urgency and hesitancy, but did not consider his urinary volume unduly large. In recent years he had noted occasional generalized pruritus, increasing weakness and fatigability.

Physical examination revealed an obese man who was pale and appeared mildly and chronically ill. The blood pressure was 186/104 mm. Hg and the weight 250 pounds. In the area of the right lobe of the thyroid was a firm, irregular mass about 4 to 6 cm. in diameter which pushed the trachea to the left and extended beneath the right clavicle. There was no abdominal tenderness. The testes were absent (removed one year previously because of suspected prostatic carcinoma); and the prostate was slightly irregular, but not large. The remainder of the physical examination was within normal limits.

The laboratory data revealed the hematocrit to be 45 per cent, white blood cells 7,200 per cu. mm. and the stools were negative for blood (guaiac). The urine specific gravity was 1.010 to 1.012 with a trace

of protein and an occasional white blood cell in sediment. Phenolsulfonphthalein excretion was 60 per cent in two hours. The electrocardiogram revealed left axis deviation and inversion of T1 and Tv5 without decrease of the Q-T interval. Relevant blood and urine analyses performed during hospitalization are recorded in Table III. The serum concentrations of sodium, potassium, chloride and total protein were normal. X-ray films of the chest revealed a slightly enlarged heart, and those of the upper gastrointestinal tract showed a moderate-sized hiatus hernia. Roentgenographic survey of the skeleton showed no evidence of any abnormality.

Because of the long history of nausea and epigastric discomfort together with the history of renal colic, a serum calcium determination was obtained. This was found to be elevated, and the serum phosphorus concentration was low. (Table III.) Slit lamp examination of the eyes, performed by Dr. Frank B. Walsh, demonstrated an opaque band at both the temporal and medical aspects of the right cornea and a few crystals in the conjunctivae of both eyes, these observations being interpreted as evidence of previous hypercalcemia [37].

During the first eight days in the hospital the patient complained of progressive nausea and headaches with occasional vomiting. The serum calcium concentration increased to 20.6 mg. per cent with a concomitant slight increase in the blood non-protein nitrogen. There was no decrease in urine output (the patient had been encouraged to drink large volumes of liquid). Because of the alarming increase in serum calcium

concentration and the development of lethargy, increasing anorexia and nausea, immediate surgical exploration for a parathyroid tumor seemed indicated. Operation was performed by Dr. James R. Cantrell, and a huge cystic parathyroid adenoma measuring 6.5 by 4.0 by 5.5 cm. was removed from the right side of the neck.

Postoperatively the serum calcium concentration gradually returned to normal, but the serum phosphorus concentration remained low. Nausea and vomiting ceased during the first few days after operation. The blood non-protein nitrogen continued to rise after removal of the parathyroid tumor, but had decreased to 54 mg. per cent when the patient was discharged from the hospital on the seventh postoperative day. The blood pressure, which had been persistently elevated before operation, was noted to be normal throughout the postoperative period of hospitalization. When the patient was seen fourteen months after operation, the blood pressure was 130/85 mm. Hg, blood non-protein nitrogen was 33 mg. per cent, phenolsulfonphthalein excretion was 60 per cent in two hours and the serum concentrations of calcium and phosphorus were normal. He had continued to have some postprandial epigastric discomfort which was probably caused by the hiatus hernia.

Comment: Although this patient's symptoms were not as severe as those of the preceding patient, they were sufficiently characteristic to suggest that the syndrome associated with marked hypercalcemia was present, and prompt operation seemed indicated. During hospitalization this patient was ambulatory, so some factor other than immobilization must have accounted for the progressive hypercalcemia. The abrupt change to normal blood pressure after operation is a unique observation for which we have no explanation.

CASE III. B. McG. (B. C. H. No. 208509), a sixty-five year old white woman, was admitted to the hospital on January 13, 1956, with the chief complaint of recurrent abdominal pain of four weeks' duration. For fifteen years she had been troubled with constipation, and for several years had complained of pains in the knees and left hip. Five months before admission she first noted anorexia, weakness, fatigue, headache, dizziness and exertional dyspnea. During the three months before entry her constipation became more obstinate, and on three occasions she went to different hospital emergency rooms where she received enemas and was discharged without further investigation. Two months before admission she began to have occasional nausea and vomiting. Four weeks later there was an abrupt onset of severe, cramping, right upper quadrant abdominal pain radiating across the epigastrium; this pain was relieved by vomiting. Subsequently the

pain recurred at frequent intervals, was located in the right or left upper quadrants of the abdomen, usually followed ingestion of food, and was often relieved by vomiting. There was no hematemesis. She had lost 10 pounds in weight in four weeks. For two weeks she had noted some cough with mucoid sputum. Because of the increasing severity of her symptoms she sought hospitalization.

On admission the blood pressure was 160/80 mm. Hg. The patient was poorly nourished and showed evidence of weight loss and dehydration. She was lethargic, and occasional generalized twitching was noted. There were small white and gray exudates in the optic fundi. A nodule was palpated in the region of the right lobe of the thyroid. The heart was not enlarged; the heart sounds were barely audible, and there was a harsh systolic murmur heard over the precordium but loudest in the fourth left interspace. The abdomen was slightly protuberant and soft; the liver was palpable 1 cm. below the right costal margin, but there was no tenderness or other abdominal masses. Physical examination was considered to be otherwise normal.

The laboratory data revealed the hematocrit to be 36 per cent, white blood cells 9,800 per cu. mm. with normal differential; ten days later the white blood cell count was 33,300 per cu. mm. Urine was acid, contained a trace of protein, and in the sediment were many hyaline and granular casts with 5 to 6 white blood cells per high power field. A stool was negative for blood (guaiac). Cerebrospinal fluid pressure, protein concentration and cell count were normal. The blood chemical determinations are recorded in Table III. The electrocardiogram revealed depressed ST segments in leads II and V₆ with normal Q-T intervals. X-ray film of the chest showed nodular infiltration and several areas of radiolucency in the left upper lung field with increased markings and pleural thickening at the right apex; these findings were thought to be due to tuberculosis of undetermined activity. A repeat x-ray film of the chest eight days later demonstrated the same abnormalities and, in addition, some haziness at the right base interpreted as possibly indicating pneumonia. A barium enema study was normal.

The patient received 2,000 to 3,000 ml. of fluid intravenously each day. She became slightly more alert during the first three days in the hospital, but thereafter became progressively more lethargic. Continued vomiting prevented x-ray study of the upper gastrointestinal tract. On the fifth hospital day fever developed, and penicillin therapy was begun. After seven days in the hospital numerous coarse rhonchi and rales were noted over both lung fields. She became afebrile, but more stuporous, finally comatose, and died on the tenth hospital day.

A postmortem examination was performed. A large parathyroid adenoma consisting almost entirely of chief cells and weighing 11.0 gm. was found posterior

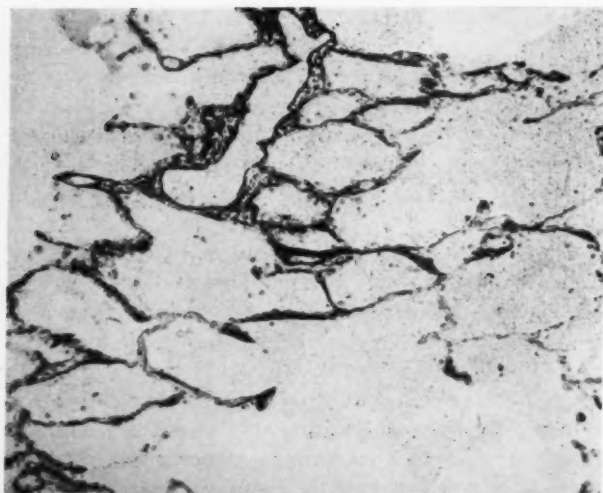


FIG. 1.* Extensive calcification of alveolar septa indicated by black areas (von Kossa stain). Original magnification, $\times 125$.

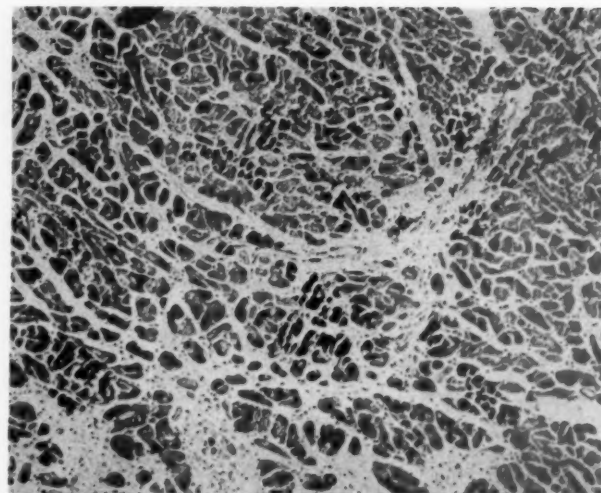


FIG. 2. Multiple foci of calcification in the myocardium. Original magnification, $\times 105$.

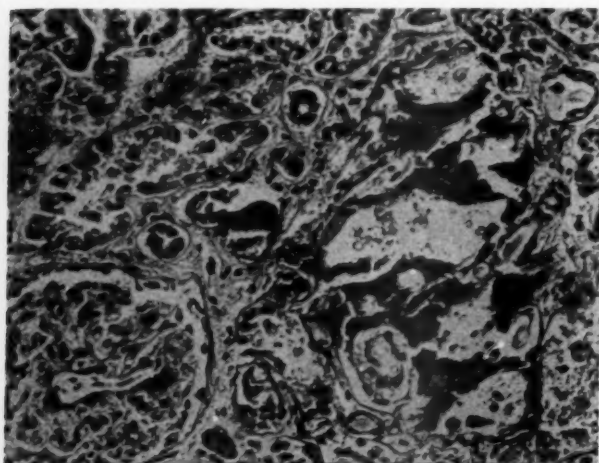


FIG. 3. Renal tubular calcification. Also shown is a glomerulus containing calcium deposits. Original magnification, $\times 265$.

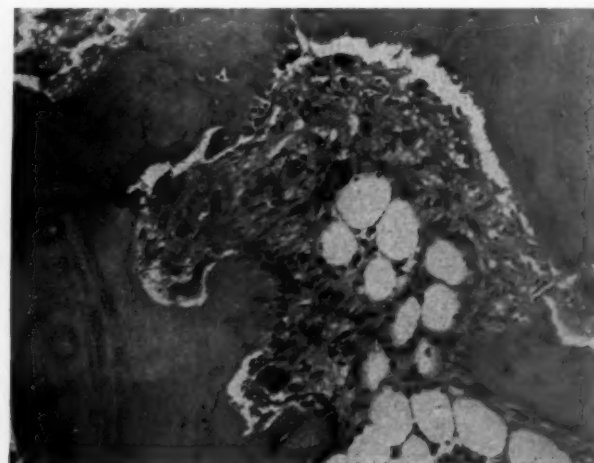


FIG. 4. Bone section demonstrating osteitis fibrosa with numerous giant cells. Original magnification, $\times 200$.

to the right lobe of the thyroid gland. There was widespread calcification involving the media of arteries and arterioles, the stroma of the gastric mucosa, the lungs, heart and kidneys. Examination of the lungs revealed emphysema and chronic fibrous pneumonitis with calcification in the alveolar septums (Fig. 1); there was no evidence of tuberculosis, but there was bronchopneumonia in the lower lobes bilaterally and multiple, small, pulmonary emboli in the right lung. Moderate hypertrophy of both ventricles of the heart with calcium deposition in the heart valves and in the myocardium was present. (Fig. 2.) The degree of coronary atherosclerosis was slight. Calcification of the renal tubular epithelium was extensive, and focal calcific deposits were noted in occasional glomeruli and in the interstitial tissues. (Fig. 3.) There was

* We are indebted to Dr. Abou Pollack for the illustrations in this report.

generalized osteoporosis with osteitis fibrosa of the ribs and vertebrae. (Fig. 4.) Other findings included chronic and focal acute pancreatitis with old peripancreatic fat necrosis, cholelithiasis and small colloid adenomas of the thyroid.

Comment: This patient manifested chiefly gastrointestinal symptoms, lethargy and progressive azotemia without significant hypertension. The correct diagnosis was not considered until two hours before death, when blood was drawn for determination of serum calcium; the result being reported several hours after the patient died. The nodule palpated in the neck was in fact the parathyroid tumor. On reexamination of the x-ray films, some generalized rarefaction of the bones was apparent; this might have been

a clue to the diagnosis had it been noted originally. The histologic changes in the kidneys did not appear advanced and might not have interfered with survival of the patient for several years if the parathyroid tumor had been removed.

This patient's course is analogous to many of the fatal cases recorded in Table I. It was fear of just such a consequence that dictated the urgency of operation in Cases I and II.

COMMENTS

In 1925 Collip, Clark and Scott [38] reported the effect in dogs of repeated injections of parathyroid extract. In this and subsequent reports [39,40] it was observed that dogs so treated became weak and anorexic, and vomiting, diuresis, diarrhea, and melena developed which was followed by oliguria, progressive stupor and death. These manifestations usually developed whenever serum calcium concentrations were greater than 15 mg. per cent. During administration of parathyroid extract there was a progressive increase in serum calcium concentration to about 20 mg. per cent, often with a decline in concentration prior to death despite continued hormone injections. Preceding death there was also an increase in concentrations of serum phosphorus and non-protein nitrogen. Similar observations have been made by other investigators [41,42] who, in addition, demonstrated a decrease in the percentage of diffusible calcium and phosphorus of the serum prior to death of animals treated with parathyroid extract [41].

The pathologic changes observed in fatal instances of hyperparathyroidism in animals and in man are similar. In the animal studies [41-44] typical lesions have consisted of microscopic areas of necrosis in cardiac muscle, kidneys (particularly in tubules), pancreas, and occasionally in the gastric and duodenal mucosa, media of arteries and skeletal muscle. Visceral congestion and petechial hemorrhages were usually present. Soft tissue calcification was most apt to be evident if hypercalcemia had existed for several days and often seemed localized to areas of necrosis. Thrombosed vessels were frequently noted, but it could not be ascertained that the areas of tissue necrosis were consequent to thrombosis of adjacent vessels [41].*

* That these features are not unique to hyperparathyroidism is evidenced by the analogous soft tissue changes observed in vitamin D intoxication of animals [45].

thyroidism recorded in Table I the clinical history was remarkably uniform. Postmortem examination of these patients revealed widespread soft tissue calcification and osteitis fibrosa. In addition some patients had necrosis in the pancreas, kidney tubules and cardiac muscles [17,18]. Focal necrosis of the liver, peptic ulceration and visceral congestion were also observed [19,21,23]. Several authors emphasized the presence of recently formed vascular thrombi [18,19]. Many of these pathologic features were present also in Case III described herein.

Some insight into the pathogenesis of acute fatal hyperparathyroidism is possibly afforded by the studies on colloidal calcium phosphate formation in the blood. That such a substance may be formed in plasma *in vivo* or *in vitro* by increasing sufficiently the concentration of either calcium or inorganic phosphorus seems well established [46]. McLean and Hinrichs [47] reported that the addition of inorganic phosphorus to dog serum (*in vitro* or *in vivo*) resulted in a reduction in the ionized calcium concentration with the formation of a physiologically inactive compound (postulated to be colloidal calcium phosphate). By *in vivo* studies they demonstrated that, once formed, this compound rapidly disappeared from the circulation. This disappearance may be effected by the macrophages of the liver and spleen, for demonstrable particulate material containing calcium and phosphorus appears in these cells after administration of large amounts of calcium or phosphorus [48].

In more recent studies Hopkins, Howard and Eisenberg [49], using the Laviets' technic of ultrafiltration, demonstrated that at high serum calcium concentrations (usually near 20 mg. per cent or greater) there was a reduction in ultrafilterable serum phosphorus. If both the serum calcium and phosphorus concentrations were increased sufficiently, there was a reduction of ultrafilterable calcium as well as phosphorus. Application of this technic to a study of serums from patients with hypercalcemia [50] showed the ultrafilterable phosphorus of four such patients to be reduced (one of these subjects had hyperparathyroidism). In these four patients vomiting, drowsiness, oliguria and azotemia were prominent clinical features. The reduction in ultrafilterable phosphorus (and frequently calcium) was thought to be most probably due to the formation of a colloidal calcium phosphate complex. These authors

TABLE IV
ULTRAFILTRATION OF SERUM FROM PATIENTS E. F. AND M. G. (CASES I AND II)

Case and Patient Initials	Date	Serum Calcium (mg./100 ml.)	Filtrate Calcium (mg./100 ml.)	Calcium in Filtrate (per cent)	Serum Phosphorus (mg./100 ml.)	Filtrate Phosphorus (mg./100 ml.)	Phosphorus in Filtrate (per cent)	When Performed
Case I, E. F.	11/19/55	18.1	3.9	4.2	108	8 days preoperatively
	11/27/55	18.0	12.6	69	3.3	2.4	73	Day of operation
	12/ 9/55	8.3	6.0	72	2.9	3.3	114	Postoperatively
Case II, M. G.	12/ 5/55	19.1	13.5	70	2.5	2.3	90	2 days preoperatively
	2/ 7/57	10.2	7.2	70	4.0	4.4	110	Postoperatively

suggested that this colloidal substance might be responsible for the particular symptoms noted in their four patients and, in agreement with others [57], for the similar clinical manifestations in previously reported cases of "parathyroid poisoning" and severe vitamin D intoxication.*

In view of the above hypothesis the determinations of ultrafilterable serum calcium and phosphorus in two of the patients of the present report were of interest. (Table IV.) In Case I the phosphorus concentration of serum ultrafiltrate obtained several days before development of intense nausea, vomiting and drowsiness was 108 per cent of that in the serum; on the day of operation ultrafilterable phosphorus was reduced to 73 per cent, whereas twelve days postoperatively it was normal (114 per cent).† In Case II ultrafilterable phosphorus was only slightly reduced (to 90 per cent) two days before parathyroidectomy, but was normal (110 per cent) in serum obtained fourteen months after operation. The ultrafilterable calcium of the serum was normal (approximately 70 per cent) in these two patients both before and after operation. Serum for ultrafiltration was not available from the third patient.

The significance of a reduced ultrafilterable calcium and/or phosphorus in patients with marked hypercalcemia is unknown. Although such a reduction may be due to the formation *in vivo* of hydroxyapatite crystals [53], or other substances of colloidal size [46], it is difficult to conceive how this might induce the particular

* Although these symptoms most often develop with serum calcium concentrations of 18 to 20 mg. per cent, some patients tolerate even higher concentrations without such manifestations [52], while in others they may occur at lower calcium concentrations [29].

† With this technic of ultrafiltration [49] the concentration of phosphorus in the ultrafiltrate of normal serum is approximately 113 per cent of the concentration in the serum. This value of greater than 100 per cent is largely due to the Donnan equilibrium effect.

clinical features encountered in these patients. Low concentrations of calcium have been shown to inhibit activity of certain mitochondrial enzymes *in vitro* [54]; but whether or not hypercalcemia causes enzyme inhibition *in vivo* is unknown, and there are at present no data showing the effect of hypercalcemia on intracellular calcium concentrations. Thus, adequate explanation of the syndrome associated with extreme hypercalcemia must await further investigation.

Identical clinical manifestations as have been described in severe hyperparathyroidism may develop in a variety of other hypercalcemic states. The coexistence of persistent nausea and vomiting, progressive lethargy and azotemia has been noted in patients with hypervitaminosis D [55], carcinoma [56,57], sarcoidosis [58], multiple myeloma [59], leukemia [60], Paget's disease [61] and in certain instances of acute bone atrophy of disuse [62,63]. As the degree of hypercalcemia, irrespective of the etiology, appears to be the determining factor, it is appropriate to designate this syndrome as "hypercalcemic crisis."

The development of this clinical state in association with marked hypercalcemia indicates a potentially fatal outcome, and therapy of such patients should be immediately directed to measures which will lower serum calcium and phosphorus concentrations. Correction of dehydration with parenteral fluids increases the survival time in experimental hyperparathyroidism [38,42] and has also been shown to improve markedly the clinical status of some patients with hyperparathyroidism exhibiting the forementioned features [26,37]. That such measures may be insufficient to alter the progressive course was demonstrated by Cases I and III of this report. In reviewing the reported instances of severe hyperparathyroidism, it is noteworthy that frequently the onset of symptoms associated with marked hypercalcemia seemed to

follow immobilization of the patient [16-32]. This apparent effect of immobilization on such patients has been noted by others [30] and certainly seemed a factor in Case I and possibly in Case III. Immediate surgical exploration for a parathyroid tumor, even in the presence of additional factors increasing the operative risk (Case I) is the only certain way of correcting the hypercalcemia and is indicated in this group of patients.

In immobilized patients with Paget's disease or acute bone atrophy of disuse in whom the syndrome of hypercalcemic crisis develops, mobilization may be all that is needed to reduce the serum calcium concentration to normal [61-63]. Parenteral fluid therapy may also prove beneficial [61]. The use of cortisone or ACTH is an additional measure helpful in the correction of hypercalcemia. Although *not uniformly effective*, administration of cortisone or ACTH results in a lowering of the serum calcium concentration in most hypercalcemic states [64,65].* However, in our experience, and in that of others, the hypercalcemia due to hyperparathyroidism has *not* been corrected during treatment with these hormones [64,65].

SUMMARY

A potentially fatal course characterized by rapidly progressive nausea, vomiting, lethargy and azotemia is occasionally encountered in patients with hyperparathyroidism. Three such patients having these manifestations are reported. In two, recognition was sufficiently prompt, and an emergency removal of a parathyroid adenoma resulted in a successful outcome in each. In the third patient the correct diagnosis was suspected only two hours before death.

Similar clinical manifestations occur with marked hypercalcemia of any etiology. Although the pathogenesis of this syndrome is not clearly understood, successful treatment seems dependent on prompt reduction of the high serum calcium concentrations.

Acknowledgment. The authors wish to express their appreciation to Dr. Theda Hopkins for

* In this clinic, cortisone in divided dosage of 300 mg./day for one day, 200 mg./day for five days, and then 100 mg./day for seven days has reduced the hypercalcemia in most patients so treated. Larger doses have been no more effective, and smaller amounts may be sufficient.

assistance in performing the serum ultrafiltrations and to Mr. Harry Eisenberg and Miss Mary Jordan for the chemical determinations.

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Phosphate Clearance in the Diagnosis of Parathyroid Dysfunction*

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APPRECIATION of the frequency of parathyroid dysfunction and of the variability of its manifestations has focused new attention upon the importance of the laboratory in diagnosis. Two recent reviews have shown that neither hypercalcemia [1] nor hypophosphatemia [2] is sufficiently marked in many instances of hyperparathyroidism to provide diagnostic security.

Although the abnormal urinary excretion of phosphorus has been extensively investigated in connection with studies of parathyroid physiology, only recently has the measurement of urinary phosphorus been utilized in the diagnosis of hyperparathyroidism. The studies of Crawford and his associates [3] indicated that the ratio of reabsorbed to filtered phosphate might be used as an index of parathyroid activity. Sirota [4] provided evidence of significant depression of tubular phosphate reabsorption in two patients with hyperparathyroidism. Schaaf and Kyle [5] further demonstrated the value of measurement of the per cent tubular reabsorption of phosphorus in the diagnosis of hyperparathyroidism and the usefulness of this technic has since been repeatedly confirmed [1,2,6].

In the diagnosis of parathyroid deficiency, on the other hand, this method is of limited value because the per cent tubular reabsorption of phosphorus is normally so high that further elevation is difficult to evaluate. Errors in the measurement of creatinine, moreover, introduce a major obstacle to utilization of phosphate reabsorption determinations as a routine test. Finally, additive errors may be involved in analyses of two different substances, and the sum might well exceed the variability resulting from measurement of a single substance. These considerations led us to a study of the value of measurement of phosphate clearance in the diagnosis of parathyroid dysfunction, since this

would obviate some of the difficulties inherent in the estimation of per cent tubular reabsorption of phosphorus.

MATERIALS AND METHODS

Control studies were made in normal hospital personnel and ambulatory patients without bone or renal disease. The patients studied included some with hyperparathyroidism, hypoparathyroidism, osteomalacia and uremia. All subjects were given a diet providing a normal intake of calcium and phosphorus for at least five days prior to testing. Those patients whose mineral intake had been severely restricted for long periods were allowed an unrestricted calcium and phosphorus intake for at least two weeks before any studies were made.

Clearances were obtained over two- to four-hour periods in the fasting state during the forenoon. Sufficient hydration was provided before and during urine collection to promote urine output ranging from 5 to 10 ml. per minute. Blood samples, drawn midway in the collection period, and urine specimens were measured for phosphorus and creatinine as described previously [5]. Phosphate clearance (Cp) and endogenous creatinine clearance (Ccr) were estimated by dividing minute excretion by serum concentration in mg./ml. Correction for surface area was made in only two patients with rickets who were of very short stature. Estimation of the per cent tubular reabsorption of phosphorus (per cent TRP) was obtained either by subtraction of urinary phosphate excretion from the estimated filtered load ($Ccr \times \text{serum P}$) or from the ratio Cp/Ccr [5,7].

RESULTS

Figure 1 demonstrates the per cent TRP in six patients with hyperparathyroidism and seven patients with parathyroid deficiency as compared with the normal range of reabsorption in 25 normal subjects. Phosphate reabsorption was significantly depressed in all instances of hyper-

* From the Department of Medicine, Georgetown University Medical Center, and the Georgetown Medical Division of the District of Columbia General Hospital. This study was supported by the William Wade Hinshaw Cancer Research Fund.

function but was normal or only minimally elevated in hypoparathyroidism.

Clearance values for phosphorus in twenty-five normal subjects who were studied during the fasting state in the forenoon are shown in Figure 2A, the mean value being 10.8 ± 2.7 , and the

one patient who had renal failure with uremia and an endogenous creatinine clearance of only 30 ml./min. Phosphate clearance in ten patients with hypoparathyroidism was diminished, ranging from 1.7 to 7.3 ml./min. In five patients with osteomalacia Cp was significantly elevated. Two

TABLE I
PHOSPHATE CLEARANCE (C_p) IN HYPOPARATHYROIDISM
BEFORE AND DURING TREATMENT WITH VITAMIN D₂

Treatment	No. of Patients	Cp (ml./min.)	
		Range	Mean
None.....	10	1.7-7.3	5.0
Vitamin D ₂	8	1.8-7.8	5.7

range from 6.3 to 15.5 ml./min. The range of phosphate clearance in four other normal subjects who had multiple studies on different days and at intervals during the same day is depicted in Figure 2B. The greater variation and somewhat higher clearance values noted in these four subjects are probably attributable to the fact that some measurements were conducted during the afternoon when phosphate clearance is apt to be higher than in the morning [8].

In Figure 3, phosphate clearance in the normal subjects is compared with that noted in various types of parathyroid dysfunction. In hyperparathyroidism Cp was elevated except in

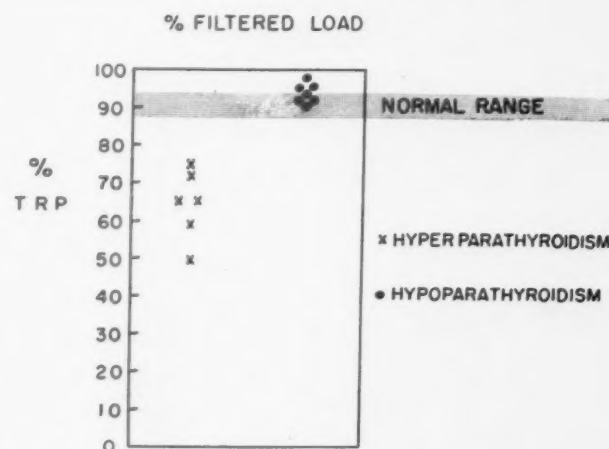


FIG. 1. Per cent of filtered phosphorus reabsorbed in normal subjects and patients with parathyroid dysfunction.

of these patients had hypocalcemic rickets and were presumed to have secondary hyperparathyroidism. The others demonstrated multiple tubular defects suggesting the presence of a primary defect in the tubular reabsorption of phosphorus.

Figure 4 illustrates the effect of intravenous administration of 200 to 400 units of parathyroid extract on phosphate clearance in normal sub-

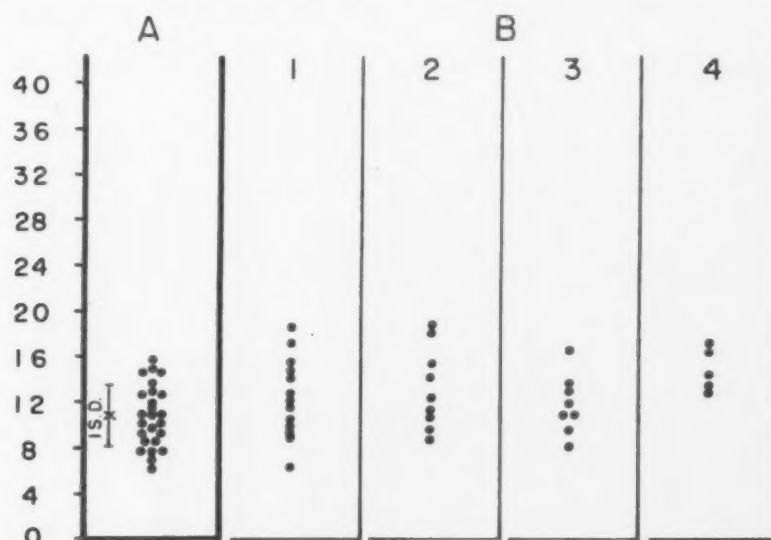


FIG. 2. Phosphate clearance: A, forenoon measurement in twenty-five normal subjects; B, measurement at different times during the day and on different days in four normal subjects.

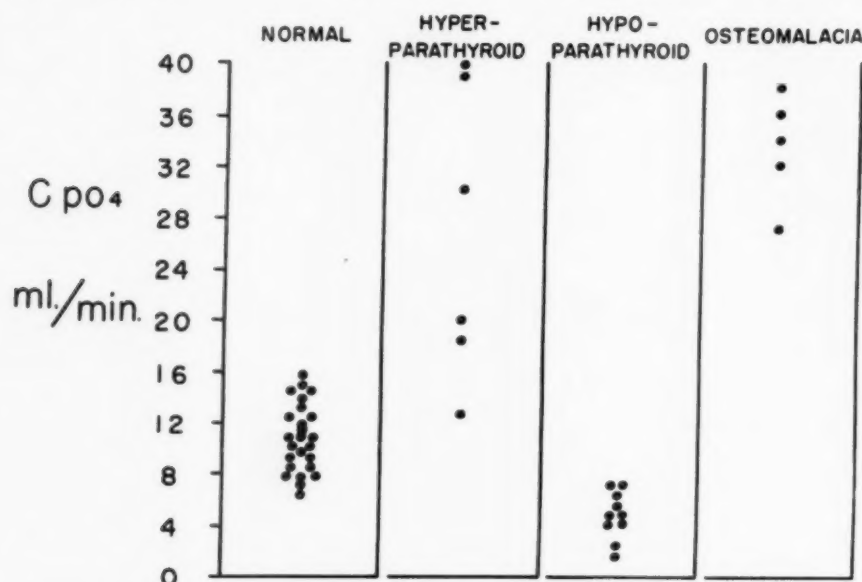


FIG. 3. Comparison of phosphate clearance in hyperparathyroidism, hypoparathyroidism and osteomalacia with that of normal subjects.

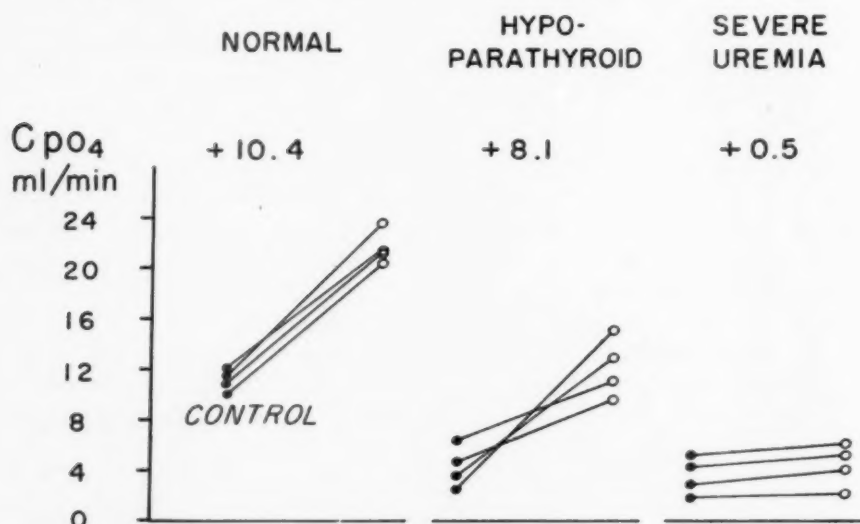


FIG. 4. Influence of parathyroid extract on phosphate clearance.

jects, in instances of hypoparathyroidism, and in severe renal disease. The control and post-injection clearance values are the averages of two hourly collection periods before and two or three hourly collection periods after the injection of parathyroid extract. In the normal subjects parathyroid hormone induced a significant increase in phosphate clearance, and the very low Cp in the patients with hypoparathyroidism was elevated to within the normal range. Although the patients with uremia had very low phosphate clearance, comparable to that noted in parathyroid deficiency, no appreciable elevation resulted from the administration of parathyroid hormone.

Table 1 compares the phosphate clearances in untreated instances of parathyroid deficiency with those of patients whose blood calcium and phosphorus had been brought to or toward normal with vitamin D₂ therapy. No significant difference in phosphate clearance was noted between the untreated and the treated patients.

Figure 5 depicts the changes in per cent tubular reabsorption of phosphorus and in phosphate clearance following the removal of a parathyroid adenoma. The sharp fall in Cp was as striking as the rise in per cent TRP. These changes, occurring in the face of continued hypophosphatemia and a constant endogenous creatinine clearance, are clearly indicative

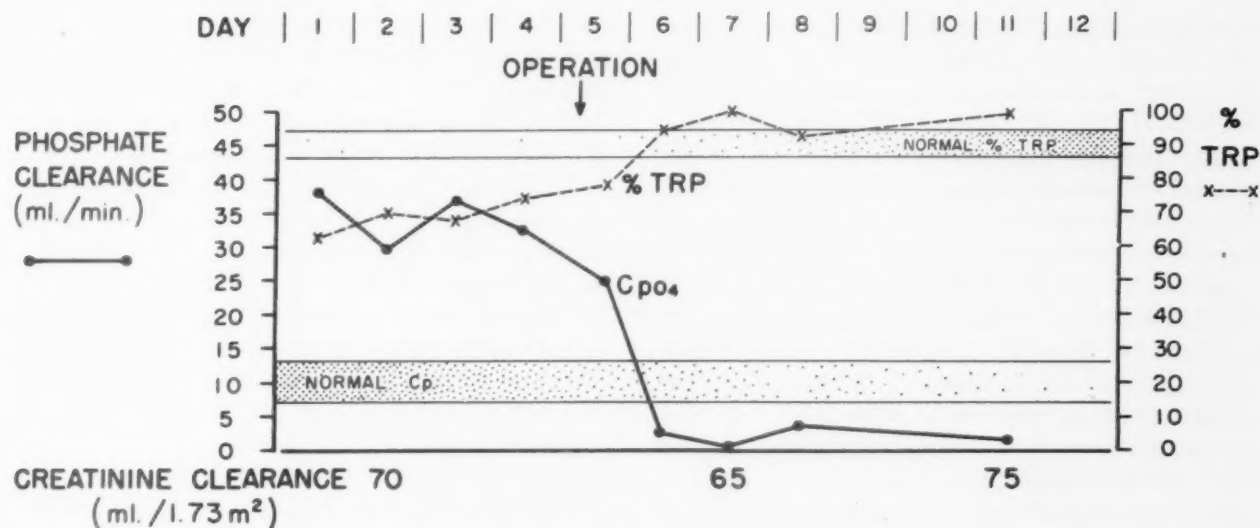


FIG. 5. Changes in phosphate clearance and phosphate reabsorption following removal of a parathyroid adenoma.

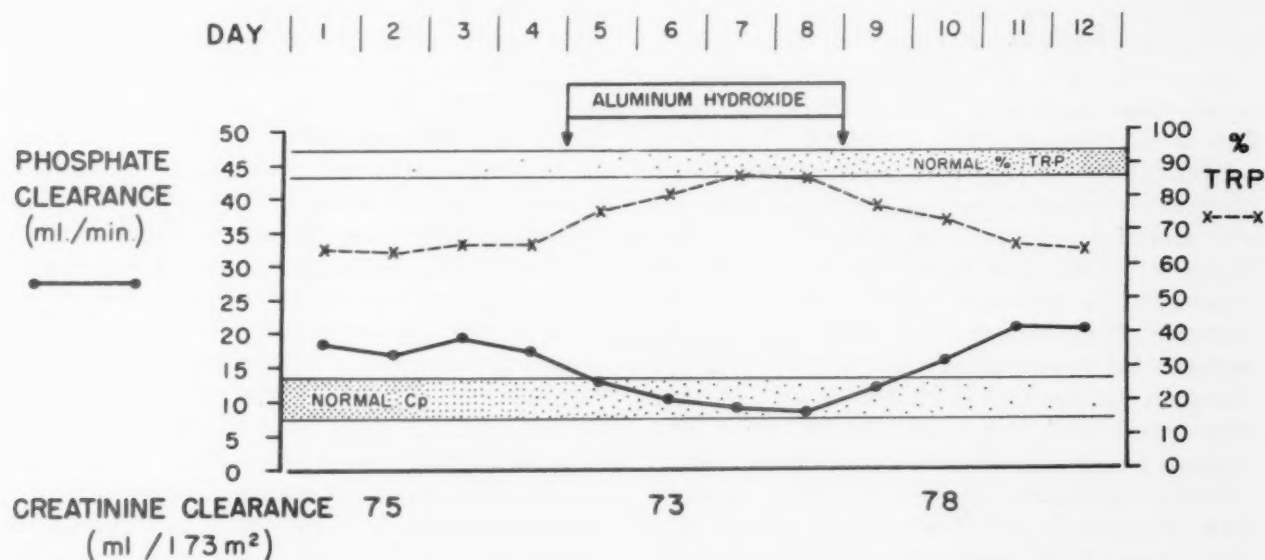


FIG. 6. Changes in phosphate clearance and phosphate reabsorption induced by inhibition of phosphate absorption in the gut.

of enhancement of tubular reabsorption of phosphorus.

Figure 6 demonstrates the importance of diet on such indices of parathyroid function as per cent TRP and Cp. This woman had renal calculi, hypercalcemia and hypophosphatemia coupled with the low per cent TRP and elevated Cp consistent with hyperparathyroidism. The administration of aluminum hydroxide in sufficient doses (120 cc./day) to bind phosphorus in the intestinal tract and thus prevent its absorption resulted in prompt reversion of per cent TRP and Cp to normal levels. Similar return to normalcy of Cp has been observed in patients with hyperparathyroidism after institu-

tion of the low calcium and phosphorus diet applied routinely in the management of renal calculi [9].

COMMENTS

Although the plasma inorganic phosphate can be measured with a high degree of accuracy, and appears to be completely filterable at normal serum concentrations, its renal clearance shows considerable variation. Comparable variability has been associated with measurement of the maximal tubular reabsorption of phosphate (TmP). While there has been some opinion to the contrary [10], most studies indicate a definite TmP both in dogs [11] and in man [12],

even though the tubular capacity for reabsorption of phosphate varies from individual to individual and, apparently, even in the same individual [13]. Anderson [12] has pointed out that phosphate clearances are variable when the plasma phosphorus concentration is near the "threshold" value but under the conditions of our study (forenoon and fasting) the TmP is apparently well in excess of the filtered load. Under such conditions approximately 90 per cent of the filtered phosphorus is reabsorbed; consequently the phosphate clearance will be more markedly affected by changes in tubular reabsorption than by variations in the filtered load of phosphorus.

Relatively limited data have been reported on phosphate clearance in normal subjects, and it appears probable that measurement at different times of the day and under variable conditions of fasting and feeding has tended to magnify the normal variation. Ollayos and Winkler have shown that there is a wide variation in phosphorus excretion over the daily twenty-four-hour period [8] and Schaaf has demonstrated that both serum phosphorus and urinary phosphate excretion are lowest during the early morning hours [14]. Dean and McCance [15] found Cp in adults to range from 8.9 to 38.4 ml./min. with an average of 18.0 ml./min. per 1.73 square meters; the lower values were obtained in the forenoon. In the study of Blatherwick [16], Cp determined during the fasting state ranged between 4.1 and 16.3 ml./min. with an average of 8.1 ml./min. The unusually low clearances noted by Lambert et al. [17], which averaged 4.2 ml./min., may have been the result of unduly short periods of collection; it may also be noted that their data included a number of serum phosphorus determinations well below the accepted range of normal.

Levitan [18] demonstrated a decrease of phosphate reabsorption and doubling of Cp during intense hyperglycemia. Although the degree of hyperglycemia was greater than would be expected in the usual absorptive state the possibility that recent feeding might influence Cp, not only by affecting the level of serum phosphorus but also because of competition of amino acids at the tubular reabsorptive site, must also be considered. This possibility is strengthened by the observation of Ollayos and Winkler [8] who noted that the increased rate of phosphorus excretion which followed feeding was not associated with a change in serum phosphorus

concentration. Consequently it would appear that the average value for Cp noted in our studies, 10.8 ml./min., is of the same order of magnitude as that of other observations conducted under the same conditions.

Phosphate clearance appears to be very low in the newborn, particularly in infants receiving human milk. McCrory and his associates [19] demonstrated a relatively high rate of phosphorus excretion, considering the low filtration rate, which they attributed to a high serum phosphorus and a low rate of tubular reabsorption. Infants receiving cow's milk, with its relatively higher phosphorus content, have a higher Cp than those receiving human milk. Gardner and his co-workers [20] demonstrated that the very low Cp of infants receiving human milk could be doubled by administration of a high phosphorus diet, but that normal adult values were not attained. It appears that with the rapid maturation of tubular function, adult values for phosphate clearance are attained in very early childhood [21].

Crawford and his associates [3] first suggested that the ratio of reabsorbed to filtered phosphorus could be used as an index of parathyroid function. Milne, Stanbury and Thomson [22] used a similar approach by calculation of the ratio of phosphate clearance to that of creatinine before and during phosphate infusion. Sirota [4] reported impairment of phosphate reabsorption in two patients with hyperparathyroidism, as determined by clearance ratios of phosphorus and inulin; removal of the parathyroid adenomas resulted in significant decrease of the clearance ratio, the filtration rate remaining constant. Schaaf and Kyle [5], and others [1,2,6], have demonstrated the feasibility of applying measurement of per cent tubular reabsorption of phosphorus to the diagnosis of hyperparathyroidism.

However, two basic difficulties have arisen in the clinical application of this test: (1) properly timed urine collections, and (2) apparent difficulty in obtaining accurate creatinine determinations. The first difficulty is readily circumvented by establishing adequate urine flow which will reduce errors due to "renal dead space" and minimize those which result from inexact timing of the collection period. Nordin and Fraser [23] have called attention to the fact that the ratio of urine phosphorus to urine creatinine, upon which depends estimation of per cent TRP, can be derived from an untimed

urine collection. In our opinion this is a totally unsatisfactory solution of the problem. Impairment of glomerular filtration will depress per cent TRP, and inaccuracy of the creatinine determination will shift the per cent TRP in either direction. Consequently it is necessary to determine the creatinine clearance not only to assess the degree of renal dysfunction but also to ascertain the possibility of gross inaccuracy in methodology whenever the ratio of reabsorbed to filtered phosphorus is determined.

The second problem, the frequency with which technical inaccuracy leads to erroneous creatinine determinations, has no simple solution. Unless proper precautions are taken and duplicate analyses are made no reliability can be placed on these measurements.

Determination of serum and urine phosphorus is much more accurate than that of creatinine, suggesting that determination of phosphate clearance would be more suitable for general use. Our studies indicate that, with one exception, Cp was sufficiently in excess of the normal range to provide diagnostic aid in our cases of hyperparathyroidism. The single exception was the patient shown in Figure 3 who had severe impairment of glomerular filtration as manifested by an endogenous creatinine clearance of 35 ml./min., and blood urea nitrogen levels of 35 to 40 mg./100 ml. The per cent TRP was decreased, as would be expected at this level of impaired glomerular filtration, and thus was of no diagnostic value. The studies of Goldman and Bassett [24] indicate that phosphate clearance is well preserved until the glomerular filtration rate drops to less than 25 ml./min. When severe renal failure ensues, measurement of either per cent TRP or Cp would be of dubious value in the diagnosis of hyperparathyroidism. However, the finding of a low Cp in the presence of a lowered ratio of filtered to reabsorbed phosphorus would point to renal disease rather than to hyperfunction of the parathyroids. On the other hand, presence of a normal or only slightly depressed Cp in conjunction with azotemia and a low per cent TRP should heighten suspicion of parathyroid hyperfunction and in this situation measurement of Cp should provide diagnostic help. In those vexing cases in which coexistence of hyperparathyroidism and renal disease makes it necessary to determine cause and effect relationships no single test is diagnostic. Thus it would appear that measurement of Cp, which is technically simpler than

that of per cent TRP, is of diagnostic value in hyperparathyroidism, particularly when coupled with measurement of the blood urea nitrogen.

Phosphate clearance is increased also in osteomalacia, both of the vitamin D deficiency and renal tubular varieties perhaps because of secondary hyperparathyroidism in some instances of the former and possibly as a result of a tubular "phosphate leak" in the latter. Only on rare occasions should there be any difficulty in distinguishing between primary hyperparathyroidism and osteomalacia [25]. We have also observed increase in Cp in Cushing's syndrome, multiple myeloma and, to a much lesser degree, in hyperthyroidism. Mahler and Stanbury [26] noted increased phosphate clearance in an instance of potassium-losing renal disease. Return of Cp to normal levels after potassium therapy suggested that diminished tubular reabsorption of phosphorus may be induced by potassium depletion.

Nordin and Fraser [27] have introduced an interesting approach to measurement of abnormalities of phosphate reabsorption by calculation of the "phosphate excretion index." Although valuable in demarking phosphate reabsorption at various levels of serum phosphorus, it does not, as far as we can determine, offer any material advantage over the simpler calculation of phosphate clearance and, moreover, requires measurement of creatinine.

As noted previously (Fig. 1), the magnitude of the normal per cent TRP renders further increase of little value in the diagnosis of parathyroid deficiency. Determination of phosphate clearance, however, appears to have considerable usefulness in this regard. Although there was some overlap with the normal, Cp was uniformly and in most instances significantly depressed in hypoparathyroidism, as shown in Figure 3. Milne [28] noted a low Cp in an instance of idiopathic hypoparathyroidism and a lesser degree of depression of Cp in an instance of postoperative parathyroid deficiency; in both instances Cp was increased to normal levels or above by the administration of parathyroid extract.

The observation, summarized in Table 1, that Cp remains significantly depressed after therapy of hypoparathyroidism with vitamin D₂ is apparently due to a continued enhanced rate of tubular phosphate reabsorption which maintains the serum phosphorus at a high normal level. This finding lends itself to practical

application. The effects of vitamin D₂ may persist for several months after termination of therapy. Consequently, when the original diagnosis of hypoparathyroidism is in question, or the possibility of recovery of parathyroid function under consideration, there has been no alternative but to discontinue treatment, maintain clinical observation, and conduct measurements of serum calcium and phosphorus for many months. Measurement of Cp should provide a proper diagnostic appraisal even during vitamin D₂ therapy. It should be pointed out, however, that the measurements summarized in Table 1 were performed after the patients had been stabilized on treatment. It might be expected that Cp would increase during the initial phase of therapy with vitamin D₂, perhaps because of an increase in filtration rate [29]. Dihydrotachysterol (AT-10) is said to have an action akin to that of parathyroid hormone in promoting phosphate excretion. In one patient with hypoparathyroidism under therapeutic control with this compound, Cp again was found to be well below the normal level.

Despite the accumulated evidence of many years of study, some investigators appear reluctant to accept a renal tubular action of parathyroid hormone [30]. Some of this reluctance is apparently based on resistance to the concept of a duality of function, for a direct action of parathyroid hormone on bone has been firmly established [31,32]. The difficulty seems to arise, in part, from studies conducted so long after the phosphaturic effect of parathyroid hormone had waned that no tubular influence could be anticipated [33]. Some disbelief has apparently evolved from measurements of the effect of parathyroid hormone during phosphate infusion, an experimental design that so increases phosphate clearance as to obscure the inhibitory effect of parathyroid hormone on phosphate reabsorption [33,34]. The most vigorous dissenters apparently lean heavily on the demonstration of a non-specific phosphaturic effect of a commercial parathyroid extract [35]. It therefore must be emphasized that the association of increased phosphate clearance with the low serum phosphorus of hyperparathyroidism, and decreased clearance with the high serum phosphorus of hypoparathyroidism, offers strong suggestive evidence that a physiologically significant parathyroid regulatory mechanism for renal excretion of phosphate is operative in the euparathyroid state. No other explanation ap-

pears tenable, since in these settings of parathyroid dysfunction measurement of phosphate clearance clearly defines an abnormality which seems causally related to changes in endogenous hormone.

It is important to emphasize that changes in phosphorus intake materially influence the aforementioned tests of parathyroid function. As shown in Figure 6, suppression of phosphate reabsorption in the intestine by aluminum hydroxide will, even in hyperparathyroidism, result in elevation of the lowered per cent TRP and depression of the elevated Cp. This effect is apparently completely extratubular for at the very low fixed TmP characteristic of parathyroid hyperfunction a minute decrease in the filtered load of phosphorus will cause a major decrease in phosphorus excretion. Since hyperparathyroidism is usually sought most vigorously in patients with renal calculi, the effect of limitation of dietary intake must be considered in many instances. The frequent practice of encouraging a low calcium intake will provide, in the cooperative patient, a phosphorus intake sufficiently low to give phosphate clearances in the normal range, even if hyperparathyroidism is present.

Both Milne [28] and Handler [36] have objected to the concept that the parathyroid hormone controls the ratio of filtered to reabsorbed phosphorus. As evidenced by the ease with which Cp can be influenced by change in phosphorus intake, similar objections may be offered to overemphasis of the use of Cp as an index of parathyroid activity. However, measurement of total urinary phosphorus excretion per unit of time has no more physiological significance than measurement of other urinary solutes when the physiological relationship between load and a specific tubular function is disregarded.

SUMMARY

Measurement of the ratio of filtered to reabsorbed phosphorus (per cent TRP), while of diagnostic value in hyperparathyroidism, is less satisfactory as a diagnostic test in parathyroid deficiency, and requires measurement of the glomerular filtration rate. A study was therefore made of the applicability of the simpler measurement of phosphate clearance (Cp) in the diagnosis of parathyroid dysfunction.

In twenty-five normal subjects the mean Cp, measured during the forenoon under fasting conditions, was 10.8 ± 2.7 ml./min. Except in

one patient with associated severe renal disease, Cp was substantially elevated in hyperparathyroidism. In ten patients with parathyroid deficiency Cp was significantly depressed even when the hypocalcemia was corrected by vitamin D₂ therapy.

These studies indicate that measurement of phosphate clearance is a valuable screening test for hyperparathyroidism and of diagnostic aid in parathyroid deficiency.

Acknowledgments: We are indebted to Lt. Colonel William H. Meroney and Lt. Commander Paul D. Doolan for their assistance in securing some of these data, and to Dr. George E. Schreiner for his helpful criticism of this material.

ADDENDUM

After this paper had gone to press, Dr. E. G. Herndon and his associates at the Metabolic Unit of Walter Reed Army Institute of Research secured data which indicate the value of Cp in diagnosis of hyperparathyroidism in the presence of severe renal impairment. A patient with a proved parathyroid tumor had azotemia and an endogenous Ccr of 15–17 ml./minute. The Cp was 11–13 ml./minute, in the normal range. One would anticipate a very low Cp in patients with renal disease of this severity unassociated with hyperparathyroidism, so that, as suggested in the manuscript, demonstration of a normal Cp in the presence of significant renal dysfunction appears to have diagnostic significance.

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Review

Clinical and Histologic Spectrum of the Nephrotic Syndrome*

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IN the past decade there has been a significant increase in our understanding of the mechanisms which are operative in the nephrotic syndrome. Important contributions include elucidation of the relationship of hypercholesterolemia to hypoalbuminemia [1], the measurement of aldosterone excretion in edematous nephrotic patients [2] and the calculation of albumin clearances through nephrotic glomeruli [3]. Some initial progress has also been made toward measurement of protein synthesis rates, an undertaking fraught with methodologic and theoretic hazards [4-7]. In addition, longterm studies in children [8,9] have helped to clarify the eventual fate of the young nephrotic patient, information that assumes considerable importance with the advent of new and effective therapeutic agents. In these respects and others, our understanding of the pathologic physiology of the nephrotic syndrome, and its natural history, has moved ahead of etiologic classification, morphologic pattern and clinicomorphologic correlation. This is inevitably the case when dealing with chronic disease in a relatively inaccessible organ. However, introduction of percutaneous needle biopsy as a fairly safe procedure [10] has, in part, solved the problem of accessibility.

In children with a nephrotic syndrome, etiologic considerations have, for the most part, been confined to poststreptococcal glomerulonephritis and "lipoid nephrosis." The controversy over the status of "lipoid nephrosis" as a disease *sui generis* continues to be lively [11,12] and appears unlikely to be resolved by reliance solely on postmortem observations. It is reason-

able to expect that renal biopsy will help considerably in establishing a histologic basis for lipoid nephrosis as well as in identifying the range of etiologies in nephrosis occurring in the young.

In contrast, the reported etiologies in nephrosis of the adult have accumulated at an impressive rate. On occasion, the association of a particular disease or circumstance with a nephrotic syndrome has been used to designate an "etiology" in spite of the obvious nosologic hazards involved. In any event, the clinician dealing with adult nephrotic subjects must now choose from a list of possibilities which includes poststreptococcal glomerulonephritis, disseminated lupus erythematosus, Kimmelstiel-Wilson's disease, amyloidosis prostatic obstruction [12], syphilis, malaria [13], poison oak [14], tridione and paradione administration, heavy metal poisonings, periarteritis nodosa and bilateral renal vein thrombosis. Other etiologies will doubtless appear in the future. To complicate the problem further, a significant number of patients remain who cannot be diagnosed as having any of these etiologies on clinical grounds, or conversely, who present with evidence for two or more etiologies. The decision has considerable importance, first because of the therapeutic and prognostic implications for the individual patient, and secondly for the sake of accurate classification in recording the responses to various therapies according to histologic as well as etiologic diagnoses. There is little justification for assuming that all adults with nephrosis have chronic glomerulonephritis [15]. Not only is this concept a sterile one, but the designation

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lacks any precise definition in the absence of tissue examination. But aside from these problems of etiology and therapy, there is urgent need for adequate serial descriptions of the pathologic anatomy of the kidneys of patients with nephrosis, i.e., need for a "morphologic life history."

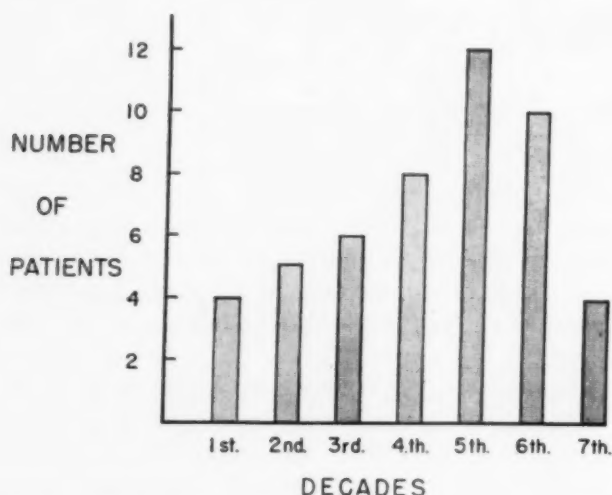


FIG. 1. Age distribution of forty-nine patients with the nephrotic syndrome.

Renal biopsy is of obvious relevance and importance to these considerations. To the immediately apparent advantages, such as nearly universal applicability and serial sampling, must be added the freedom of such tissue from post-mortem changes. In this latter regard, the appearance of the glomerular membrane is crucial and postmortem changes may account for much of the discordant opinion [17] on membranous glomerulonephritis. Electron microscopists have already taken advantage of the opportunity to study kidney biopsy specimens from five nephrotic subjects with widely differing anatomic changes as seen with conventional microscopy. The description [16] in this small group of a common pathologic denominator, involving the podocytes visible only at the level of the electron microscope, suggests not only the complexity of the problem but also the possibilities resident in newer technics.

The present study concerns forty-five patients with a nephrotic syndrome. Renal biopsy was performed in thirty-six cases and postmortem examination in the remainder. Systematic observations were made on etiologic incidence, histopathology, clinico-chemical-morphologic correlation, and, in some cases, response to treatment with adrenal cortical steroids.

MATERIALS AND METHODS

The patients ranged in age from twenty-seven months to seventy years. (Fig. 1.) Twenty-three were males, twenty-six were females. There were thirty-three Caucasians, fourteen Negroes and two Orientals. The diagnosis of nephrotic syndrome in most instances

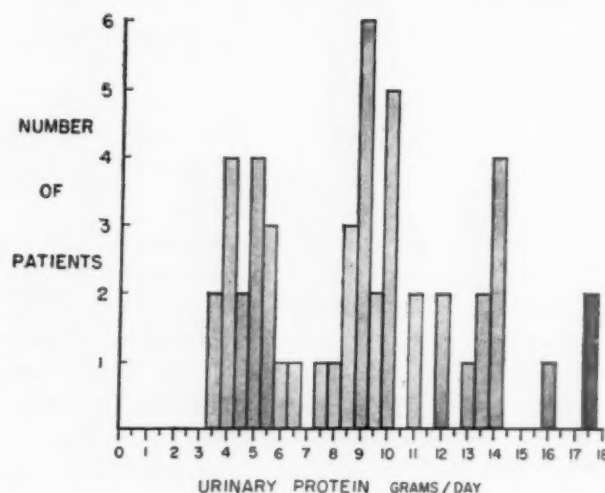


FIG. 2. Frequency distribution of urine protein losses in the nephrotic syndrome.

had been made following a diagnostic study in respect to one or more of the following: edema, proteinuria, abnormal urine sediment, and renal functional failure. Needle biopsies of the kidney were performed with a modified Vim-Silverman needle. The specifications of the needle and technic of biopsy are described elsewhere [17]. The chemical methods employed, together with normal limits for serum in this laboratory, were as follows: cholesterol (Bloor [18]): 150 to 275 mg./100 ml.; calcium (Clark and Collip [19]): 9 to 11 mg./100 ml.; urea nitrogen (Genskow [20]): 8 to 19 mg./100 ml.; total protein (Kingsley [21]): 6 to 7 gm./100 ml.; albumin (Reinhold [22]): 4 to 5.5 gm./100 ml. Twenty-four hour urinary excretion of protein was measured by the Shevky and Stafford method [23], which gives a normal upper limit of 90 mg./day.

DEFINITION

The definition of the term, nephrotic syndrome, is a matter of some confusion. To limit the designation to patients showing the classic combination of edema, proteinuria, lipiduria, hypoproteinemia and hyperlipemia, described by Leiter [24] and others, is unsatisfactory since a significant number of patients lack one or more criteria when first seen. For example, at the time of their initial workup, eleven of our forty-five patients showed no edema, ten had a serum cholesterol concentration below 275 mg./100

ml.; seven had a serum albumin concentration above 3 gm./100 ml. These groups did not overlap to any extent. In some cases continued observation revealed the development of edema or a rise in cholesterol but this was neither invariable nor predictable. On the other hand, all patients excreted at least 3.5 gm. of protein per twenty-four hours and all had double refractile fat bodies or oval fat bodies in their urine. Figure 2 reveals in fact, considerably greater protein loss in most of the group. Experience with quantitative protein excretion [25] provides satisfactory evidence that losses of the magnitude shown in Figure 2 are seldom encountered other than in the nephrotic syndrome. Two important exceptions, usually easily recognizable, are Bence-Jones proteinuria and necrotizing arteriolitis of the kidneys, the latter seen most commonly with malignant hypertension.

The nephrotic syndrome, therefore, is herein defined as a clinical state characterized by the excretion into the urine of 3.5 or more gm. of protein per day and double refractile or oval fat bodies. There is, in addition, a variable tendency toward edema, hypoproteinemia and hyperlipemia, possibly dependent upon the amount and duration of protein loss. We are well aware that the level of protein excretion may be drastically modified in either direction by treatment, changes in glomerular filtration rate and other factors, and must be interpreted with knowledge of its qualifications.

The application of special nomenclature to nephrotic subjects who lack one or another classic nephrotic feature, e.g. "pseudonephrotic" for the patient with normal cholesterol [26], must be deplored as conceptually unsound. Similarly, the term "nephrosis" [27] used alone serves only to confuse and may be retired with the honors due its age.

PATIENT PRESENTATION

The patients have been divided into eight groups on the basis of glomerular pathology as found on renal biopsy and autopsy. The absence in the present series of any consistent or marked tubular changes, such as hyaline droplets or fatty vacuolations, has been quite striking. The ages, physical findings and laboratory results shown on the charts are those present at the time the diagnosis of nephrotic syndrome was made, although in some cases previous hospital admissions or a prior history of renal disease were available. The data are presented in a uniform manner except for the group of

patients with disseminated lupus erythematosus, for reasons which are noted in the appropriate section. Figure 3, which shows a normal biopsy glomerulus on the left and a normal autopsy glomerulus on the right, provides a convenient reference for the photomicrographs to follow. The differences among glomeruli from these two sources may be quite marked and have been commented on by others [28]. The relative sizes of these groups is more likely an effect of sample size and local conditions of sampling than a reflection of the nephrotic population at large.

Group I. Membranous glomerulonephritis (ten patients, 22 per cent of forty-five histologically proved cases, ten biopsies): All patients in this group showed a diffuse thickening of the glomerular basement membrane ranging from mild to marked. The glomeruli showed no proliferative, exudative or destructive changes other than occasional hypercellularity, and the remainder of the renal parenchyma was essentially normal. A representative glomerulus is shown in Figure 4.

The patients ranged from eighteen to seventy years of age. None had any previous history of renal disease and all were diagnosed in the course of investigation for proteinuria or edema. Physical examination revealed elevated blood pressures in three patients as the only abnormality other than edema. The urine sediments all contained double refractile fat bodies and hyaline casts. Renal tubular epithelial cells were frequent, there were occasional red blood cells and glitter cells [29]. Two females (No. 2 and No. 4) had features in their history which were suggestive of disseminated lupus erythematosus but L.E. preparations were negative. Seven patients were treated with either adrenal corticotrophic hormone or adrenal cortical steroids, with excellent response (complete remission) in two, good response (persistent, mild proteinuria) in three, poor response (decrease in amount of proteinuria only) in one and no response in one.

Follow-up studies are as yet less than one year in duration in this group. In this short time there have been no deaths and no spontaneous remissions. It is noteworthy that an otherwise complete remission does not necessarily include the disappearance of double refractile fat bodies, for these may persist in the urine for long periods even when all else is normal.

The variety of clinical situations wherein a membranous glomerulonephritis may be found

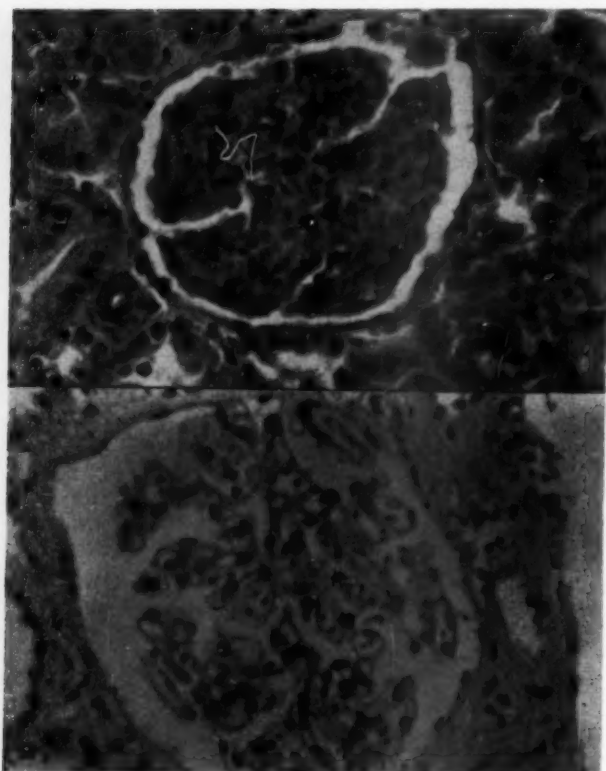


FIG. 3. Normal glomerulus from biopsy specimen (bottom) is compared with normal glomerulus from an autopsy specimen (top). Note the lacy appearance of the capillary tuft and the presence of luminal red cells in the biopsy specimen. $\times 240$.

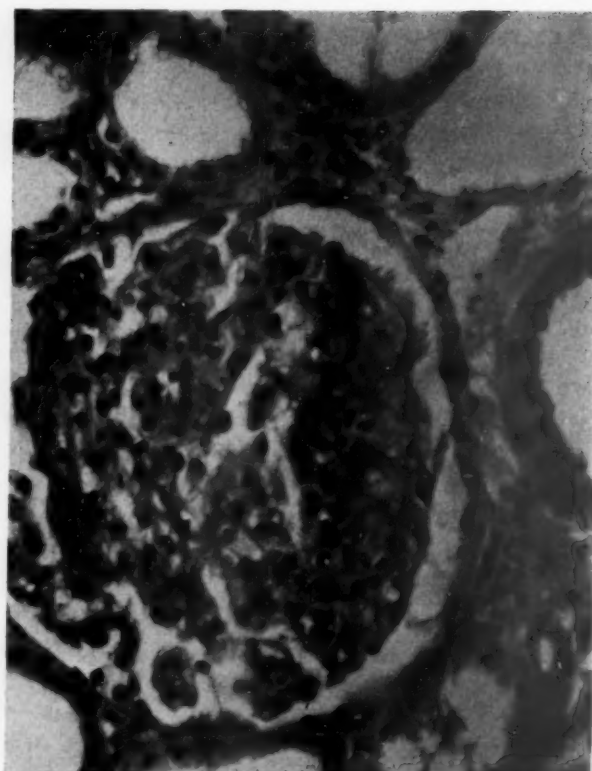


FIG. 4. Renal biopsy specimen from a nephrotic patient showing the characteristic thickening and fusion of membranous glomerulonephritis. Slight hypercellularity is also present. $\times 225$.

has been well described by Allen [17] and includes such widely varying circumstances as relapsing fever and the administration of nitrogen mustard. We may speculate that in all patients with membranous glomerulonephritis a nephrotic syndrome will eventually develop if given sufficient time. For example, we have found this lesion to be characteristic of true pre-eclampsia and one such patient, showing well-marked membranous changes on biopsy, was found to be excreting 12 gm. of protein per day for a few days after delivery, thus suggesting a "larval form" of nephrotic syndrome which is quickly reversible. The observations of Moschowitz [30] and Parrish [31] strongly suggest that the same kind of glomerular change may follow clinically typical poststreptococcal acute glomerulonephritis. Further observation may separate our ten patients into more definite groups (lupus erythematosus, etc.) but for the present their clinical and histologic similarities justify their inclusion under a single heading.

Group II. Acute and chronic glomerulonephritis (twenty-one patients, 47 per cent, thirteen biopsies, eight autopsies): Although these patients exhibited

a wide variety of clinical courses and histopathologies, certain groups may be roughly delineated as follows:

(A) A rather striking subgroup consisted of patients in whom the nephrotic syndrome came late in the course of their chronic glomerulonephritis, at a stage when renal functional failure was evident. The anatomic changes were characterized by widespread hyalinization and obliteration of glomeruli. Occasional glomeruli could be found showing membranous or proliferative changes but Figure 5 may be regarded as typical. Chronic pyelonephritis, nephrosclerosis and interstitial fibrosis were common associated findings.

Clinically, the usual picture was one of edema and proteinuria, frequently without a past history of renal disease. Upon investigation, a nephrotic syndrome with hypertension and azotemia was found. This latter point contrasts quite sharply with the previous group. Urine sediments showed doubly refractile fat bodies, broad renal failure casts, hyaline casts and frequently large numbers of glitter cells and bacteria, for superimposed pyelonephritis was com-

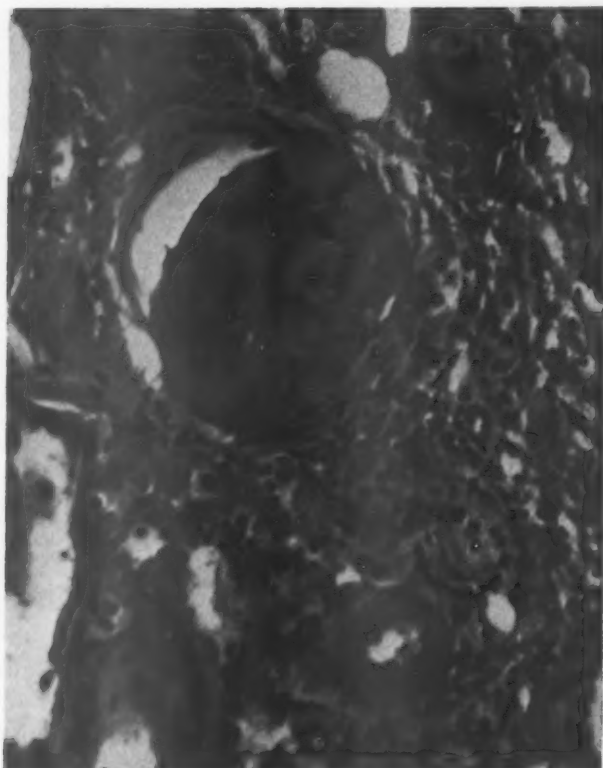


FIG. 5. Renal biopsy specimen from a nephrotic patient with chronic glomerulonephritis and azotemia. Section shows an end stage, hyalinized glomerulus. A thickened arteriole and interstitial infiltrate are also seen. $\times 240$.

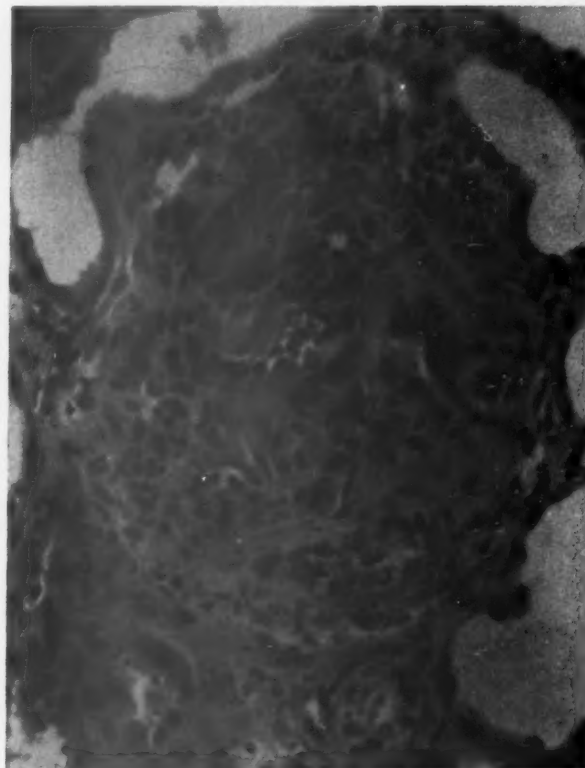


FIG. 6. Renal biopsy specimen from a nephrotic patient with active glomerulonephritis and renal failure. The changes seen are destructive, exudative and proliferative, a common combination in the nephritic-nephrotic group. Note small aneurysmal loop in the center. $\times 240$.

mon. Of the seventeen patients in this category, seven were dead of uremia within four years.

Two instances may be cited of the difficulties in making a clinical diagnosis. Patient No. 22 presented with a nephrotic syndrome and (1) a history of glomerulonephritis in childhood, (2) a positive serologic test for syphilis, (3) an abnormal glucose tolerance and (4) a suspicious L.E. cell preparation. Biopsy revealed a chronic glomerulonephritis with predominately hyalinized glomeruli, and extensive pyelonephritis. Patient No. 16 was known to have diabetes with retinitis proliferans and microaneurysms. Her nephrotic syndrome had always been considered to be on the basis of Kimmelstiel-Wilson's disease until post-mortem examination revealed a far-advanced chronic glomerulonephritis.

(B) The second subgroup of nephrotic patients with glomerulonephritis consisted of those whose disease began with a clear-cut episode of acute glomerulonephritis which persisted in an acute form. Their glomerular inflammatory disease was then complicated by a nephrotic syndrome within weeks or months.

Pathologically, the glomerular changes were

extensive and consisted of fibrinoid necrosis, polymorphonuclear infiltration, proliferation of epithelium with crescent formation and hyalinization. (Fig. 6.) These are precisely the changes which have recently been characterized [17] as being unable to "produce the clinical complex of lipid nephrosis."

Clinically, these patients were designated as nephritic-nephrotic patients in acknowledgment of their dual process—i.e., acute glomerulonephritis with its attendant hematuria, red cell casts and hypertension, as well as the various manifestations of the nephrotic syndrome. As might be expected, telescoped sediments [32] were frequently found in this group. The prognosis was poor, with renal failure and death in uremia the common mode of exit. One of these patients, a five year old boy, followed this course of events with one dramatic exception—he became totally anuric while receiving steroids and remained so for sixty days, supported by hemodialysis, until death in pulmonary edema. It is of interest that this nephrotic patient, with no protein loss for the period of anuria, did not return his serum protein or cholesterol to normal.



FIG. 7. Renal biopsy specimen from a three year old nephritic-nephrotic patient with a relatively mild clinical course. Glomerulus shows enlargement, hypercellularity and focal thickening. $\times 240$.

This nephritic-nephrotic course was followed by three patients—two children and one adult. A fourth patient demonstrated a much milder version, histologically and clinically, of the nephritic-nephrotic course. This was a three year old girl noted to have intermittent periorbital edema, "almost from birth." She was investigated at age twenty-seven months and found to have active glomerulonephritis and a nephrotic syndrome. These persisted, and at age three renal biopsy was performed. The predominant glomerular change was hypercellularity with enlargement. (Fig. 7.) Glomeruli were also found showing only membranous change, and occasionally advanced fibrosis and hyalinization. Steroids have failed to alter the course of her disease although, in keeping with the morphologic changes, the blood urea nitrogen has remained normal.

It must be emphasized that glomeruli showing membranous, proliferative, exudative, destructive and hyaline changes were all present in patients in groups II, A and II, B. There was, however, a predominant morphologic alteration which could be roughly correlated with the clinical course. As is demonstrated, the nephrotic

syndrome makes its appearance at any point during the course of glomerulonephritis, including the initial acute stages in childhood, the exacerbation of a chronic stage in adults, or the "non-inflammatory" terminal uremic stage.

Group III. Kimmelstiel-Wilson's disease (three patients, 7 per cent, three biopsies): On biopsy, all three patients showed the characteristic nodular glomerular disease of diabetes. (Fig. 8.) An important additional finding consisted of a diffuse eosinophilic thickening of the glomerular loops. Nephrosclerosis and pyelonephritis were frequently present. In these patients the nephrotic syndrome was diagnosed in the course of a study of the cause of edema and proteinuria. The duration of their diabetes varied from newly discovered to twelve years. The clinical characteristics of diabetic subjects with Kimmelstiel-Wilson's disease have been well described in recent articles [33,34], and will not be commented on here. It is of interest, however, to speculate on the relationship between morphology and the development of a nephrotic syndrome. Allen [11] suggests that the stretching of capillary membranes around the nodules may play a part in producing the abnormal permeability. It seems equally reasonable to assign the responsibility to the diffuse membranous lesion which accompanies the nodules. These were present in all three of our patients and are present in the illustration of a nodular lesion in Allen's article. It may be noted that we have biopsied non-nephrotic diabetic subjects in whom the same nodular and diffuse lesions were found. Presumably duration and other unknown factors play a part.

Group IV. Amyloid disease (four patients, 9 per cent, three biopsies, one autopsy): All glomeruli showed the same change (Fig. 9) consisting of a diffuse infiltration resulting in virtually complete replacement by a homogenous, soft appearing material which took the methyl violet stain for amyloid. The same infiltrate was found in blood vessels and deposited focally around the tubules and in tubular basement membranes. Chronic pyelonephritis in varying degree was also present. The first three patients began their clinical disease with edema and the subsequent discovery of a nephrotic syndrome. Steroids were involved in two instances. In patient No. 35 edema first developed while he was receiving steroid therapy for his chronic ulcerative colitis. Patient No. 37 had been given a course of steroids for his nephrotic syndrome without

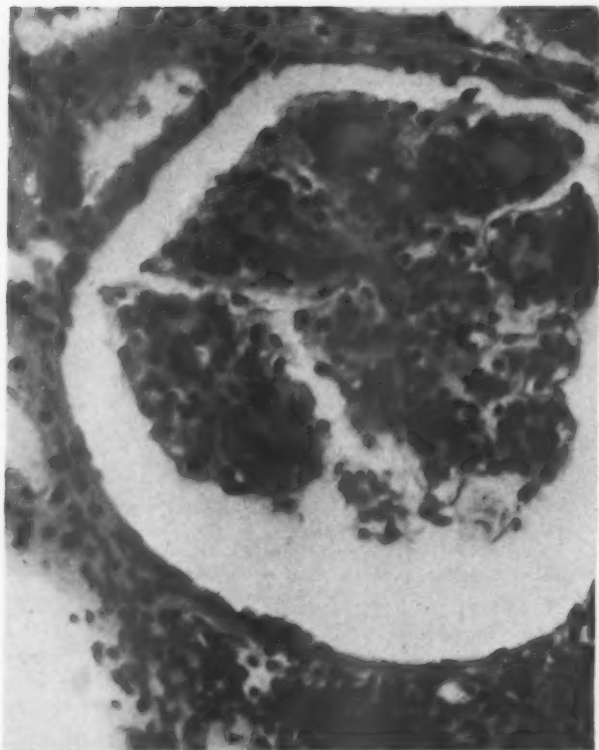


FIG. 8. Renal biopsy specimen from a nephrotic patient with diabetes mellitus, showing the typical nodular lesions of intercapillary glomerulosclerosis. There is, in addition, diffuse basement membrane thickening in the glomerulus and a marked interstitial infiltrate, produced by a coexistent pyelonephritis. $\times 240$.

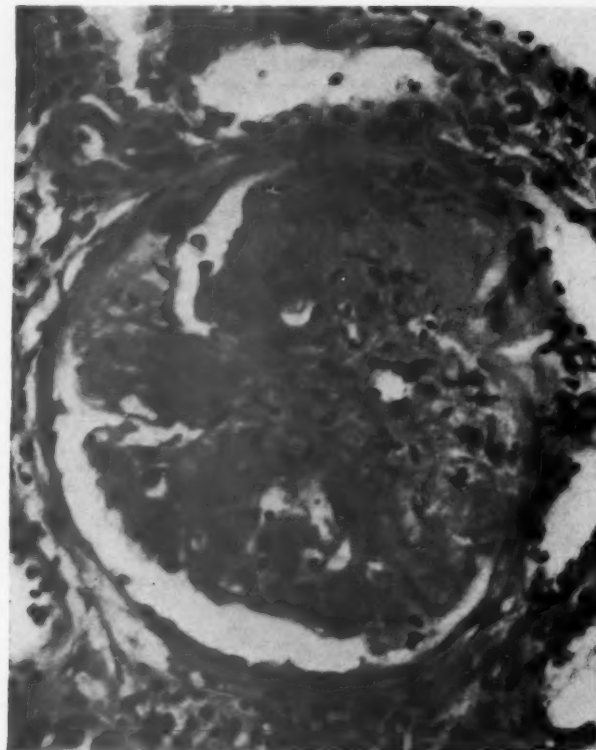


FIG. 9. Renal biopsy specimen from a nephrotic patient with "primary" amyloid disease. There is virtually total replacement of the glomerulus by a homogenous, eosinophilic material which stains with methyl violet. $\times 240$.

beneficial results. Neither patient showed a clear-cut progression or regression while receiving these drugs. Patient No. 38 was admitted with myxedema, found to be nephrotic as well, and ran a downhill course with death as a result of liver failure in three months. The other three patients died of uremia within two years.

This group of patients with amyloid nephrosis is unusual in several respects. At autopsy, none had any of the lesions usually associated with secondary amyloidosis, with the doubtful exception of chronic ulcerative colitis. Secondly, in three of the four patients the organ distribution of the amyloid as shown in Table 1 did not follow the conventional patterns of "secondary" amyloid. Thirdly, Patient No. 38 with diffuse thyroid infiltration had unequivocal clinical evidence of myxedema, thereby exhibiting the rare phenomenon of endocrine failure due to amyloid. Fourthly, contrary to traditional views, in these patients uremia developed without a clinical transition from a "pure" nephrotic syndrome into a phase characterized by hypertension and contracted kidneys. A glance at their glomerular involvement makes renal failure readily under-

standable. It is, however, perplexing indeed that such glomeruli may be not only filtering some plasma water but even molecules the size of protein.

Group V. Disseminated lupus erythematosus (four patients, 9 per cent, two biopsies, two autopsies): Interest in disseminated lupus erythematosus has increased greatly since the introduction of the L.E. cell preparation and many excellent reviews of the disease are available [35,36]. These include descriptions of renal disease and references to the nephrotic syndrome [37]. One group [25], making use of renal biopsy, has presented several anatomic variants of the kidney in lupus erythematosus. Relatively little has been written, however, on the temporal relationships of the nephrotic syndrome to the events which make up the clinical history of lupus erythematosus. With this in mind, Figures 10, 12, 14 and 16 have been constructed as follows: each figure is bounded inferiorly by a time line which begins with the first recognized manifestation of the disease. Above the time line are blocks, the upper portion of which describes the clinical events while the lower portion tabulates certain meas-

TABLE I
HISTOLOGIC CLASSIFICATION AND CLINICAL DATA ON FORTY-ONE NEPHROTIC PATIENTS

Patient	Age, (yr.), Sex	Blood Pressure (mm. Hg)	Urine Protein (gm./day)	Serum Albumin/Globulin (gm./100 ml.)	Cholesterol (mg./100 ml.)	Blood Urea Nitrogen (mg./100 ml.)	Edema	Clinical Course
<i>I. Membranous Glomerulonephritis</i>								
1.	18, F	80/60	9.1	0.9/3.1	578	13	+	Steroids, excellent response
2.	20, F	120/86	5	2.3/3.2	370	10	By history only	Steroids, good response
3.	25, F	130/100	8.3	2.7/4.1	790	13	0	Steroids, no response
4.	39, F	132/86	4	1.7/5.7	261	7	0	No treatment
5.	39, F	120/80	6.6	2.6/3.8	265	12	0	No treatment
6.	43, M	150/86	8.8	2.2/2.2	678	19	+	Steroids, poor response
7.	46, F	120/80	14	1.0/3.1	438	12	+	Steroids, excellent response
8.	48, M	140/90	11	1.7/2.8	779	14	+	Steroids, good response
9.	57, M	140/88	11	2.2/3.0	336	13	+	Steroids, good response
10.	70, M	180/90	12	2.4/2.9	619	8	+	No treatment
<i>II. Glomerulonephritis: (A) Chronic</i>								
11.	64, M	150/105	9.9	1.6/2.4	598	129	0	Supportive measures with symptomatic improvement only, 7 mo.
12.	47, F	196/120	5	2.7/2.4	340	77	+	Dead of uremia, 4 yr.
13.	29, M	122/102	14	0.9/2.7	557	37	+	Intermittently edema free on steroids, 2 yr.
14.	37, M	190/120	—	1.9/3.8	485	45	+	Unknown
15.	40, M	130/80	3.5	2.6/5.1	235	135	+	Dead of uremia, 2 yr.
16.	38, F	220/110	2.6	2.4/3.5	301	63	+	Dead of uremia, 1 yr.
17.	37, M	170/110	4.6	3.8/2.1	438	22	+	Dead, suicide while on serpasil®
18.	55, M	160/80	9	1.2/3.1	230	72	+	Edema free on steroids, 2½ years.
19.	51, M	185/95	6.2	2.9/3.5	192	120	0	Dead of uremia, 1½ yr.
20.	24, F	130/84	4.9	2.6/2.5	330	40	+	Dead of uremia, 3 yr.
21.	49, F	230/130	8.4	1.9/2.7	520	46	+	Dead of uremia, 6 mo.
22.	45, F	210/90	16	3.8/3.1	450	50	+	Dead of uremia, 2 yr.
23.	49, F	180/100	6.6	2.7/3.7	854	40	+	Edema free on mictine, 6 mo.
24.	48, M	140/90	15	2.3/3.4	532	13	+	Edema free on steroids; relapse of edema with lower dose; proteinuria persists, 10 mo.
25.	22, F	200/100	10	3.4/2.7	409	60	+	Hypertensive vascular disease chief problem; edema partially controlled with albumin, diamox®
26.	29, M	140/100	13.5	2.4/3.4	582	12	+	Unknown
27.	41, M	120/80	14	2.5/2.9	410	17	0	Diabetes mellitus developed; otherwise unchanged for past one year; no treatment

TABLE I (Continued)

Patient	Age, (yr.), Sex	Blood Pressure (mm. Hg)	Urine Protein (gm./day)	Serum Albumin/ Globulin (gm./100 ml.)	Choles- terol (mg./100 ml.)	Blood Urea Nitrogen (mg./100 ml.)	Edema	Clinical Course	
Glomerulonephritis: (B) Nephritic-Nephrotic Stage									
28.	56, M	170/90	9	3.2/3.5	168	160	+	Upper respiratory infection followed by edema and dark, foaming urine; dead of uremia within 4 mo.	
29.	5, M	120/80	5	.65/3.3	1100	17	+	Acute glomerulonephritis with development of nephrotic syndrome 1 year later; per- sistent glomerulitis; dead of uremia, 2 yr.	
30.	6, M	130/80	8	1.6/2.4	598	32	+	Acute glomerulonephritis with nephrotic syndrome; abrupt onset of anuria while on steroids; maintained 60 anuric days via dialysis; death of pulmonary edema	
31.	3, F	110/90	3.9	1.7/3.6	630	13	+	Recurrent edema from birth; persistent acute glomerulonephritis and nephrotic syndrome; refractory to steroids	
Patient	Age (yr.), Sex	Blood Pressure (mm. Hg)	Urine Protein (gm./day)	Serum Albumin/ Globulin (gm./100 ml.)	Choles- terol (mg./100 ml.)	Blood Urea Nitrogen (mg./100 ml.)	Edema	Micro- aneu- rysms	Duration of Diabetes
III. Kimmelstiel-Wilson's Disease									
32.	40, F	150/90	9.7	2.4/4.3	336	14	+	+	Diagnosed on admission
33.	59, F	160/80	12	1.9/3.6	267	23	0	+	2 yr.
34.	52, F	176/90	3.8	3.2/3.0	332	15	0	+	12 yr.
Patient	Age (yr.), Sex	Urine Protein (gm./day)	Serum Albumin/ Globulin (gm./100 ml.)	Choles- terol (mg./100 ml.)	Initial Blood Urea Nitrogen (mg./100 ml.)	Edema	Kidney Weight Right/ Left (gm.)	Organ Distribution of Amyloid	
IV. Amyloidosis									
35.	43, M	17.6	0.9/3.1	210	6	+	180/150	Kidney, adrenals, heart, bladder	
36.	54, F	5.3	1.5/3.1	1330	20	+	200/210	Liver, spleen, kidneys	
37.	61, M	15	0.9/2.8	746	21	+	130/130	Kidneys, heart, spleen, lymph nodes, pan- creas, nerves, arterioles throughout body	
38.	70, F	4	3.6/2.4	653	74	+	210/180	Kidneys, thyroid, stomach, liver, pancreas, spleen	
Patient	Age (yr.), Sex	Blood Pressure (mm. Hg)	Urine Protein (gm./day)	Serum Albumin/ Globulin (gm./100 ml.)	Choles- terol (mg./100 ml.)	Blood Urea Nitrogen (mg./100 ml.)	Edema	Clinical Features	
VI-VII. Miscellaneous									
39.	38, M	156/104	10.2	2.3/2.8	354	38	0	Homozygous hemoglobin S.; proteinuria known for 9 yr., hypertension for 2	
40.	47, M	130/70	8.3	3.2/3.3	270	6	0	Admitted with staphylococcal acute gastro- enteritis and myocardial infarction; abnor- mal sediment led to diagnosis	
41.	61, M	140/80	13.2	0.9/1.7	577	23	+	Ankle edema and proteinuria 2 yr. ago; nu- merous pulmonary and cerebral emboli	

NOTE: Patients 42 to 45 (disseminated lupus erythematosus), Group v, are described elsewhere in text.

20 YR. W ♀

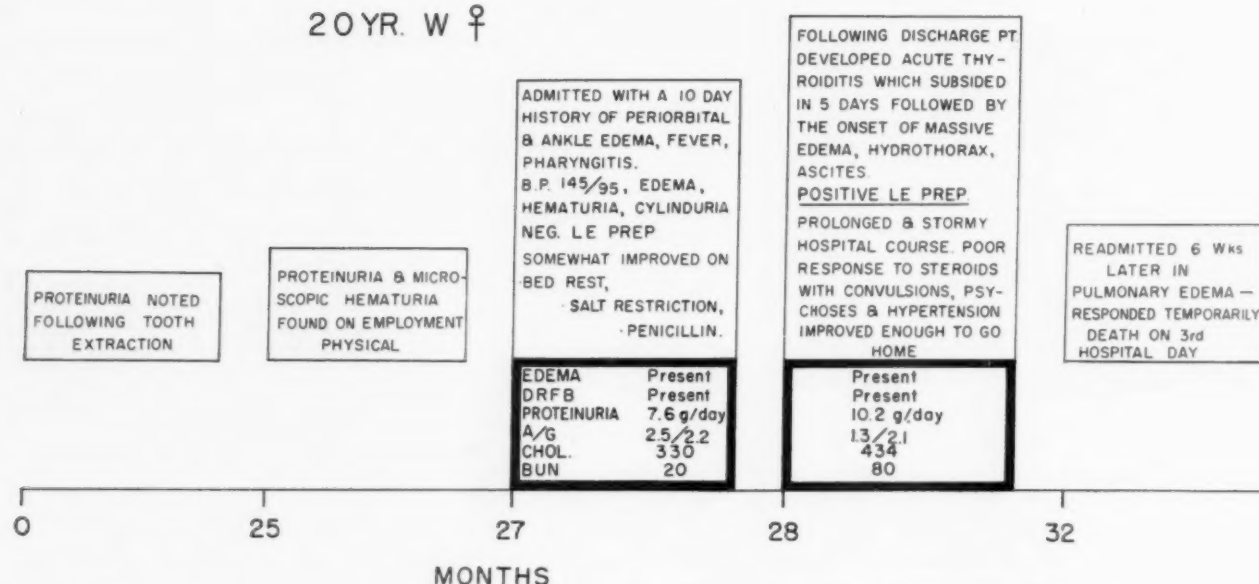


FIG. 10. Clinical and laboratory course of a twenty year old nephrotic female with disseminated lupus erythematosus. Death in renal failure within thirty-two months.

urements and observations of interest. An outlined lower box indicates the presence of sufficient evidence for a diagnosis of nephrotic syndrome. Note that the left hand margin of the blocks corresponds to that point on the time line when the observations were made. A study of

these charts and their corresponding biopsy or autopsy is interesting for the wide range of clinical courses and histology displayed.

(A) Patient No. 42 (Fig. 10) began her disease with an acute glomerulonephritis upon which a nephrotic syndrome was quickly superimposed. Her course closely resembled the nephritic-nephrotic patients of group II with unrelenting acute glomerulitis, uremia and death within eight months. The manifestations of

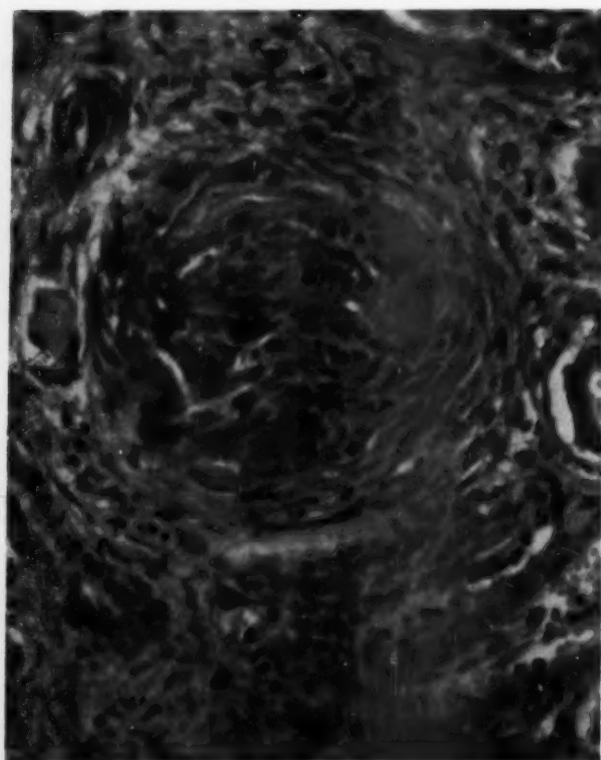


FIG. 11. Autopsy specimen from patient whose course is charted in Figure 10. Note the marked destructive and exudative changes in the glomerulus. X 240.

16 YR. C ♀

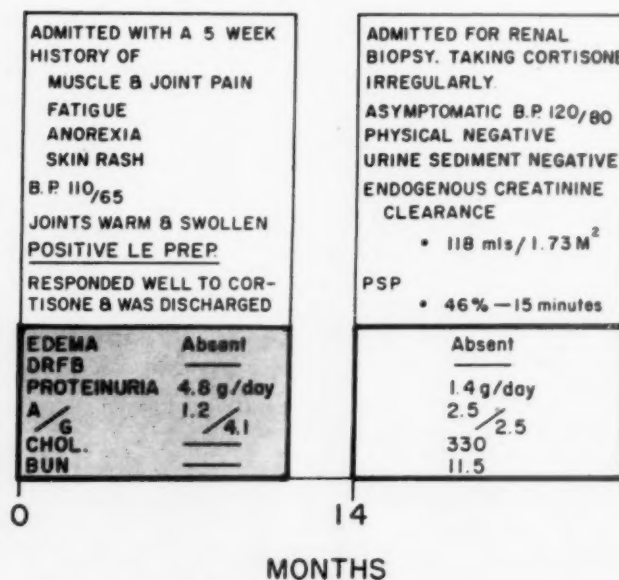


FIG. 12. Clinical and laboratory course of a sixteen year old nephrotic female with disseminated lupus erythematosus. X 240.

her disease were almost exclusively renal and, in accord with general experience, failed to respond to steroid therapy. The administration of hormone was, in fact, followed by severe psychosis, pustular acne and exacerbation of her azotemia and hypertension. Note the first appearance of a positive L.E. preparation after administration of steroid therapy. Her glomerular pathology (Fig. 11) was characterized by widespread fibrinoid necrosis and exudation.

(B) Patient No. 43 (Fig. 12) presented a more typical clinical picture for lupus erythematosus when she was first seen but she also had sufficient laboratory evidence for the diagnosis of a nephrotic syndrome. Her extra-renal disease responded quite well to steroid therapy but proteinuria persisted fourteen months later in smaller amounts. Her biopsy specimen (Fig. 13) revealed a well marked membranous glomerulonephritis with focal hypercellularity.

(C) Patient No. 44 (Fig. 14) first presented with malignant hypertension and a nephrotic syndrome. She progressed rapidly downhill with death of uremia seven months later. Renal biopsy specimen (Fig. 15) showed destructive glomerular changes with wire looping and densely eosinophilic areas of necrosis in peripheral capillary loops.

(D) Patient No. 45 (Fig. 16) had a rather extraordinary course with fulminating disseminated lupus erythematosus which began at age sixteen and responded dramatically to steroids. After forty-one months of apparently normal renal function, a nephrotic syndrome with hypertension and renal failure developed while the patient was receiving steroid therapy and quickly progressed to severe uremia. Administration of nitrogen mustard was followed by a transient diuresis but no lasting effect on the degree of renal failure. Although not shown on the chart, death occurred in the fiftieth month. Post-mortem changes in the glomeruli (Fig. 17) were predominately those of severe membranous glomerulo-

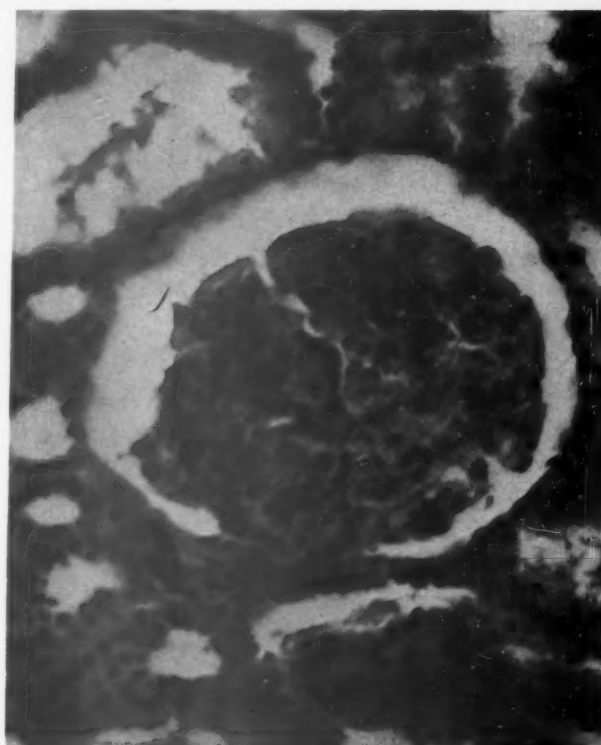


FIG. 13. Renal biopsy specimen from patient whose course is charted in Figure 12. The lesion is a diffuse membranous glomerulonephritis with slight hypercellularity.

nephritis with focal fibrinoid necrosis and occasional wire looping.

Several points are illustrated by these patients. Histologically, the changes associated with a nephrotic syndrome due to disseminated lupus erythematosus ranged from a simple membranous glomerulonephritis to a necrotizing process similar to that of group II, B. Although the

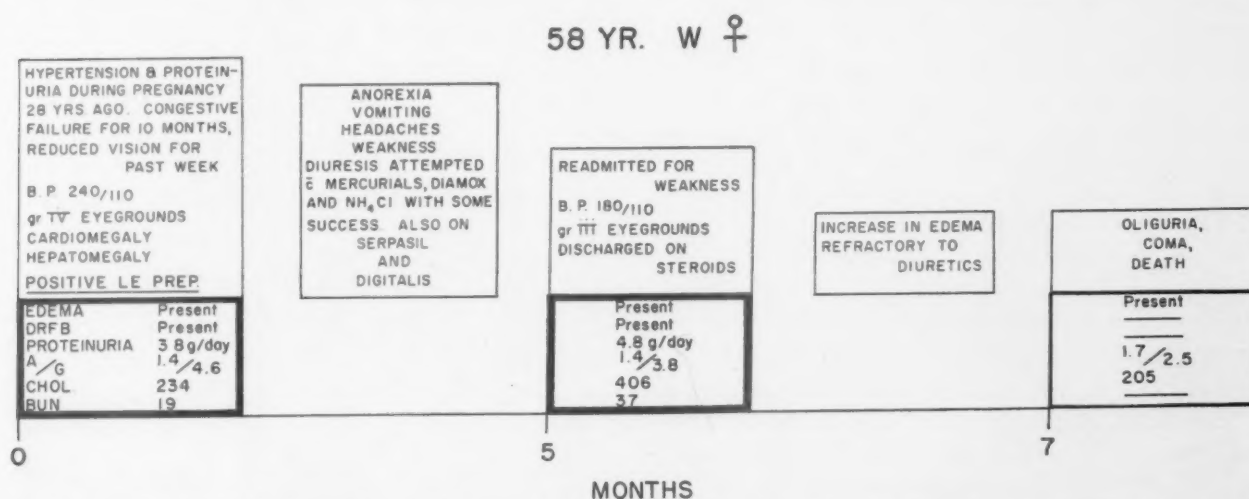


FIG. 14. Clinical and laboratory course of a fifty-eight year old nephrotic female with disseminated lupus erythematosus. Death in renal failure within seven months.

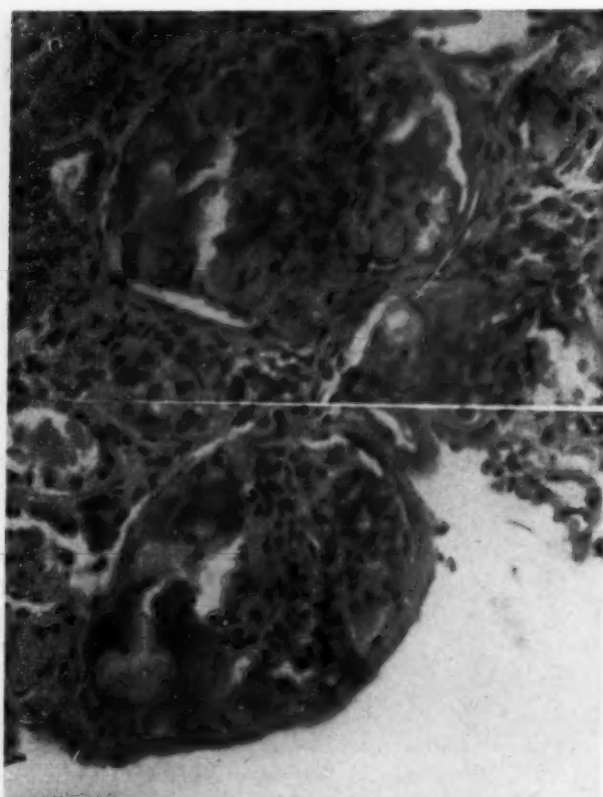


FIG. 15. Renal biopsy specimen from patient whose course is charted in Figure 14. Note destructive changes with wire looping and densely eosinophilic areas of peripheral necrosis in glomeruli. $\times 240$.

former was often accompanied by focal hypercellularity, wire looping was uncommon. The findings in these and other patients with lupus erythematosus demonstrate that the kidney of disseminated lupus erythematosus may be indistinguishable from that of poststreptococcal glomerulonephritis. The similarity to poststreptococcal disease is evident on a clinical level as well. For example, the nephrotic syndrome may occur at any time during the course of the disseminated lupus erythematosus, from very early (No. 43) to very late (No. 45). One may therefore see a "pure" or "mixed" nephrotic syndrome. Mention may be made of the great frequency of hypertension in disseminated lupus erythematosus when renal involvement is present and this may even go on to the point of malignant hypertension (No. 44). It has been our experience that steroid therapy is not likely to prove harmful in renal involvement due to disseminated lupus unless functional failure, as reflected in elevation of the blood urea nitrogen, is present. This is true even of patients with "telescoped" sediments if renal function

remains intact, as it frequently does for long periods of time.

Groups VI, VII and VIII. (Three patients, three biopsies): vi: No. 39. Patients with sickle cell disease, as well as trait, have been the subjects of recent reports describing various nephropathic manifestations such as a reversible impairment of tubular function [38] and parenchymal bleeding with gross hematuria [39]. This present report is the first description, so far as we are aware, of a nephrotic syndrome occurring in sickle cell disease. (The patient No. 39 is of considerable historical interest aside from his kidney disease [40].) The diagnosis was made in the course of an investigation of hypercholesterolemia discovered while he was the subject of another study. His biopsy specimen (Fig. 18) revealed focal glomerular lesions which were interpreted as hyaline thrombi and quite reminiscent of subacute bacterial endocarditis. Other renal changes included extensive hemosiderosis, advanced nephrosclerosis and parenchymal scarring. The patient refused both treatment and hospitalization. Ten months after biopsy he died of uremia at another hospital.*

vii: No. 40. This patient was admitted with an acute staphylococcal gastroenteritis and acute posterior myocardial infarction. He was found to have doubly refractile fat bodies in the urine. Subsequent workup disclosed a nephrotic syndrome. Renal biopsy specimen (Fig. 19) showed membranous glomerulonephritis which, in some areas, was focal in distribution. Descriptions of interstitial nephritis are rather uncommon although an authoritative discussion is to be found in Fishberg [12]. Capillary thrombosis and glomerular compression are mentioned by that author but neither a nephrotic syndrome nor glomerular lesions such as those in Figure 19 are described. We are reluctant to believe that the interstitial and glomerular lesions in this patient are coincidental in their association. Allergy to a bacterial toxin is a reasonable speculation which links the two together.

viii: No. 41. The final patient was a sixty-one year old man with a clinical history of frequent pulmonary emboli and cerebrovascular accidents. His biopsy specimen (Fig. 20) showed no definite glomerular lesions. It was thus of distinct value in ruling out several possible etiologies of a

* Since this paper was submitted, a second patient with the nephrotic syndrome and sickle cell anemia has been studied. Biopsy revealed similar but less advanced lesions of miliary infarction and focal glomerular lesions.

16 YR. C ♀

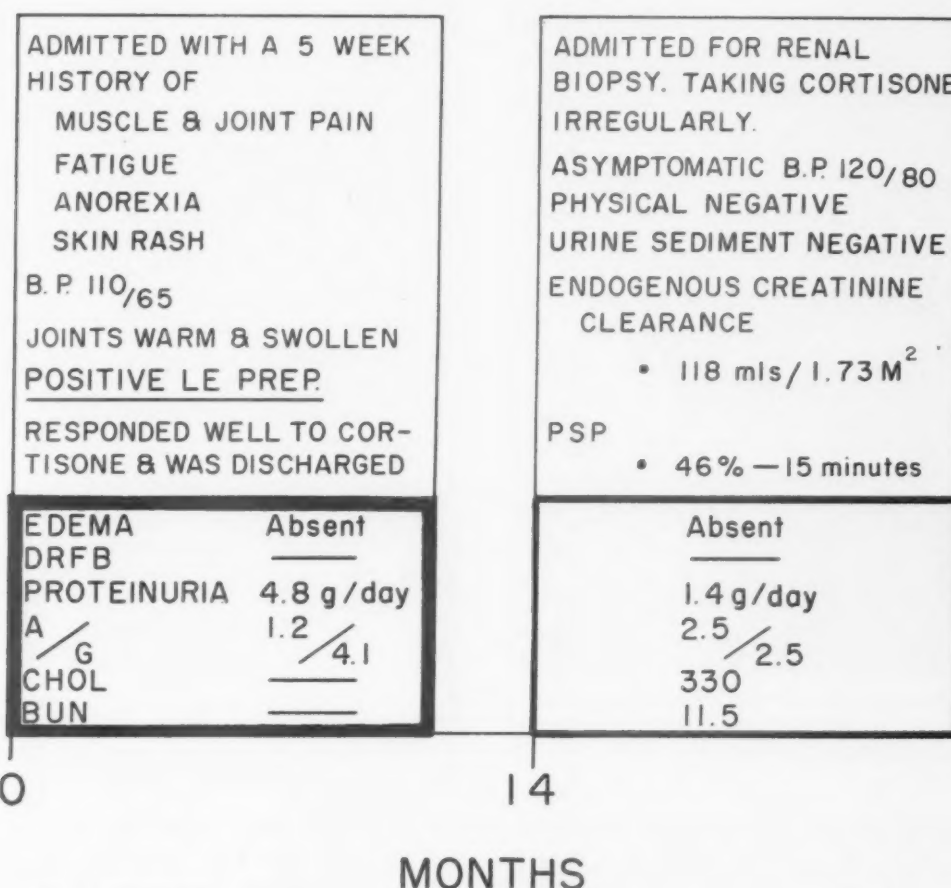


FIG. 16. Clinical and laboratory course of a sixteen year old nephrotic female with disseminated lupus erythematosus. Death in renal failure within fifty months.

nephrotic syndrome. Figure 20 is compatible with a diagnosis suggested by the patient's clinical course, i.e., bilateral thrombosis of the renal veins, if allowance is made for the fact that the mild glomerular thickening reported in other patients with nephrosis of this etiology has been seen mainly in autopsy specimens [47].

CLINICAL AND LABORATORY CORRELATION

1. An early suggestion of Addis [42] has been given new elegance and interest with the recent work of Rosenman et al. [1] on the role of serum albumin in producing the hypercholesterolemia of the nephrotic syndrome. It has been suggested that albumin acts as a transport mechanism for the egress of cholesterol from plasma to bile. A deficiency of serum albumin, therefore, leaves cholesterol trapped in plasma. In support of this, the hypercholesterolemia of the nephrotic rat has been found to be entirely confined to the plasma. Further supporting evidence has been offered in

the failure of serum cholesterol to rise when the experimental animal has been given nephrotoxic serum but prevented from exhibiting proteinuria (ureteral ligation, etc.) or prevented from lowering serum albumin concentration (by the infusion of albumin). This hypothesis suggests an inverse but not necessarily straight line relation between the serum concentrations of cholesterol and albumin. In Figure 21 the values for serum albumin have been plotted against those for serum cholesterol in forty-nine patients (includes four nephrotic patients without histologic diagnosis) excluding determinations performed while patients were receiving serum albumin or steroid therapy. The right upper quadrant representing serum albumin levels of more than 3 gm./100 ml. and serum cholesterol of more than 400 mg./100 ml. shows a striking absence of points. It may be reasoned that the points in the lower left quadrant would, in time, move to the lower right and thus conform to prediction.

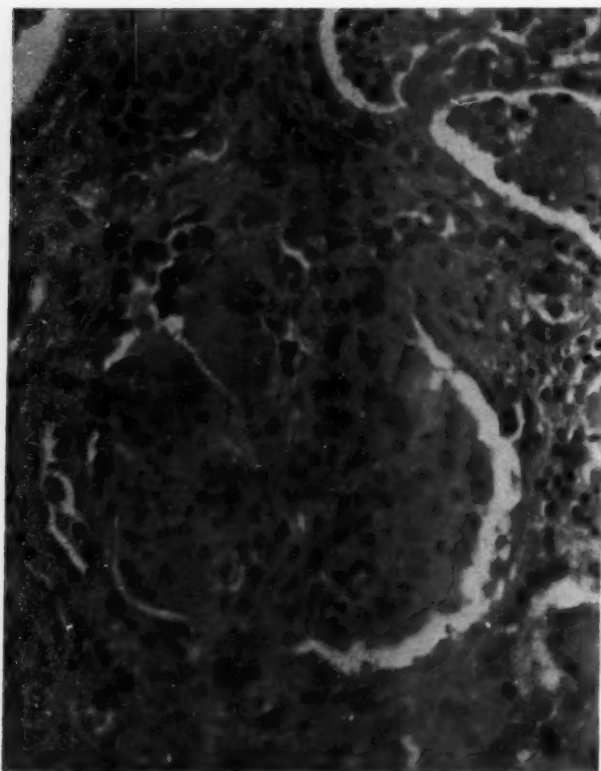


FIG. 17. Autopsy specimen of patient whose course is charted in Figure 16. Glomerulus shows mixed changes which are membranous, proliferative and lobular. $\times 240$.

These crude data are compatible with the transport block theory. Heymann's finding [43] that hyperlipemia may precede hypoproteinemia in the nephrotic rat is discordant. It seems likely that in a system as complex as that which governs the breakdown and transport of blood fat a great many factors will ultimately be defined. For example, we have noted changes in the ultracentrifuge lipid pattern of nephrotic subjects given heparin, without concurrent changes in proteinuria, renal function or clinical course. Similar findings have been noted by others [44]. The available data suggest, therefore, that nephrotic hyperlipemia is confined to plasma and is the result of physicochemical changes within the plasma rather than any more fundamental metabolic defect. In this context, the hyperlipemia may be considered a secondary manifestation of the nephrotic syndrome.

2. It may be seen from Figure 22 that all patients with massive edema had serum albumin levels below 2.5 gm./100 ml. Those with absent or slight edema showed enough scatter in their values to rule out any simple, direct relationship of hypoalbuminemia and edema. This is in keeping with *a priori* considerations [45] which place

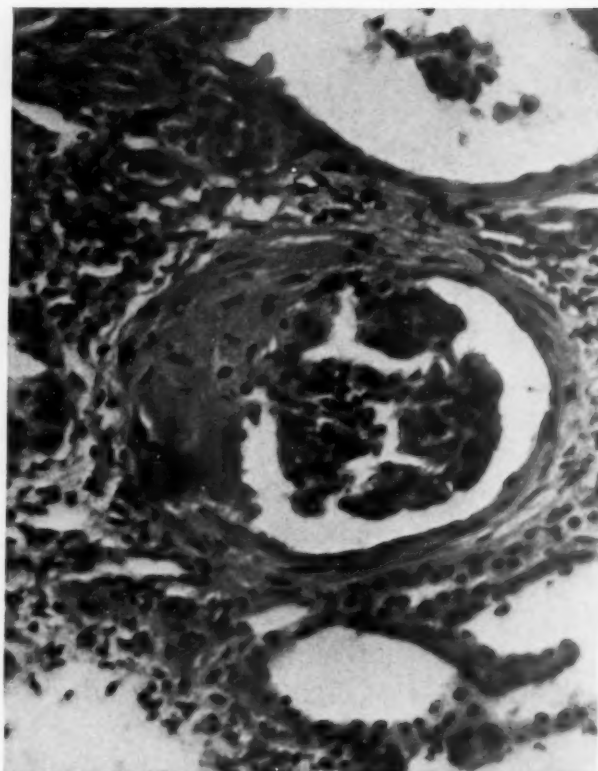


FIG. 18. Renal biopsy specimen from a nephrotic patient with sickle cell anemia showing periglomerular fibrosis, a crescent shaped area of fibrosis, membranous changes and stromal infiltrate. $\times 240$.

a sharp limitation on the amount of edema fluid which can be formed from plasma alone, no matter how low the protein. The data do suggest, however, the facilitating role which hypoalbuminemia may play in augmenting a disorder of volume regulation such as edema.

3. Erythrocyte sedimentation rates are characteristically elevated in the nephrotic syndrome regardless of etiology. This may be attributed [46] to the frequently elevated fibrinogen concentration in the serum of nephrotic patients. The mechanism of this elevation is unknown. In the present series, thirty-eight of forty-three patients had corrected sedimentation rates (Wintrobe) ranging from 20 to 40 mm. Such considerations make the sedimentation rate of little value as an index of possible inflammatory response when making an etiologic diagnosis on clinical grounds alone.

COMMENTS

The history, physical examination and laboratory findings in a patient with the nephrotic syndrome necessarily reflect both the underlying disease and the abnormalities due to the nephrotic syndrome itself. A particular patient may pre-

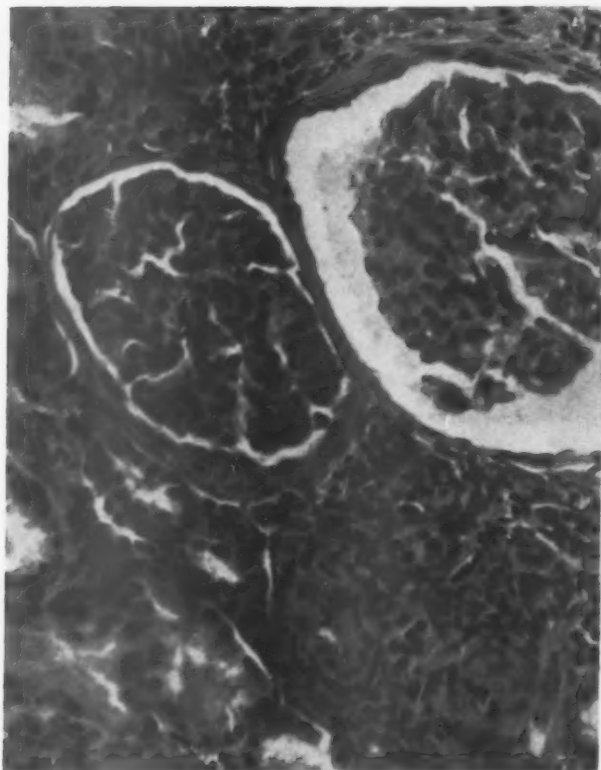


FIG. 19. Renal biopsy specimen from a nephrotic patient with acute staphylococcal enteritis and myocardial infarction. Lesions include a massive interstitial infiltrate, focal and diffuse membranous glomerulonephritis and periglomerular fibrosis. $\times 240$.

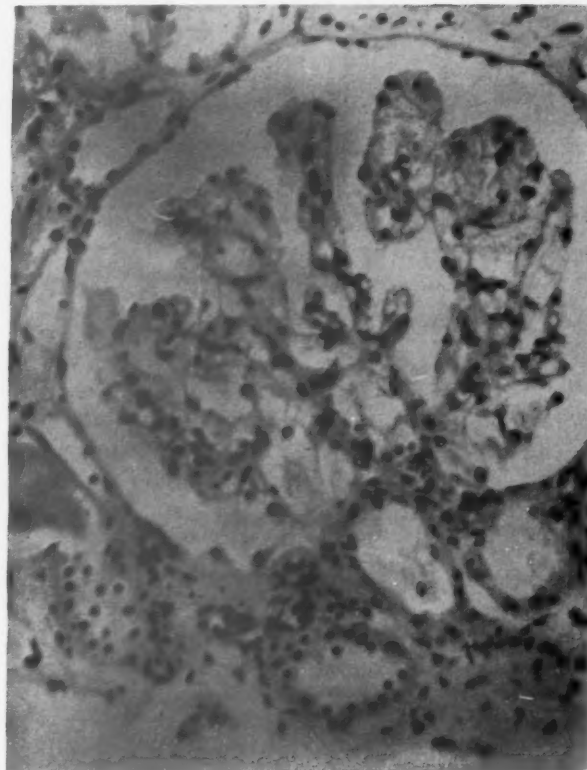


FIG. 20. Renal biopsy specimen from a nephrotic male with numerous embolic accidents. There are no pathologic changes in the glomerulus. $\times 240$.

sent, for example, with all the other manifestations of disseminated lupus erythematosus while his nephrotic syndrome remains solely a laboratory diagnosis. At the other extreme, the underlying disease may be clinically undetectable and the findings wholly attributable to the nephrotic syndrome. Such findings include a history of edema which is often quite subtle, localized to the scrotal, periorbital or pedal areas, and recognized by the patient only in retrospect. A very important group of nephrotic subjects, 24 per cent of the present series, gave no history of edema and showed none on physical examination. A history of excessive foaming and stickiness of urine may be helpful in dating the onset of massive proteinuria. On physical examination, findings due to the nephrotic syndrome consist of edema in any part of the body, retinal sheen, pallor and a recently described [47] sign of chronic hypoalbuminemia, i.e., paired white lines in the fingernails. Laboratory diagnosis rests basically on quantitative measurements of urine protein and careful examination of the urine sediment. The most constant abnormality of the sediment is the presence of doubly re-

fractile fat bodies. These are accumulations of cholesterol esters and may be found within tubular, epithelial cells, imbedded in casts or floating free. Simple methods of providing the polarized light necessary for their identification have been described [48]. Renal tubular cells and oval fat bodies are frequent; the former may be passed as casts of their parent tubules. Hyaline casts are usually numerous and are either simple or filled with various inclusions. These and other elements are illustrated and discussed in a review to be published elsewhere [49]. These findings are common to all nephrotic urines, regardless of etiology. The remainder of the sediment, however, differs from patient to patient.

Polymorphonuclear leukocytes are commonly found in the urine of patients with superimposed pyelonephritis. This is particularly frequent in patients whose nephrotic syndrome results from a chronic glomerulonephritis. Pyuria, including the glitter phenomenon [50], may also be encountered in patients with an acute glomerulonephritis without coexisting infection. The finding of red cells, red cell casts, broad renal failure casts and other formed elements is

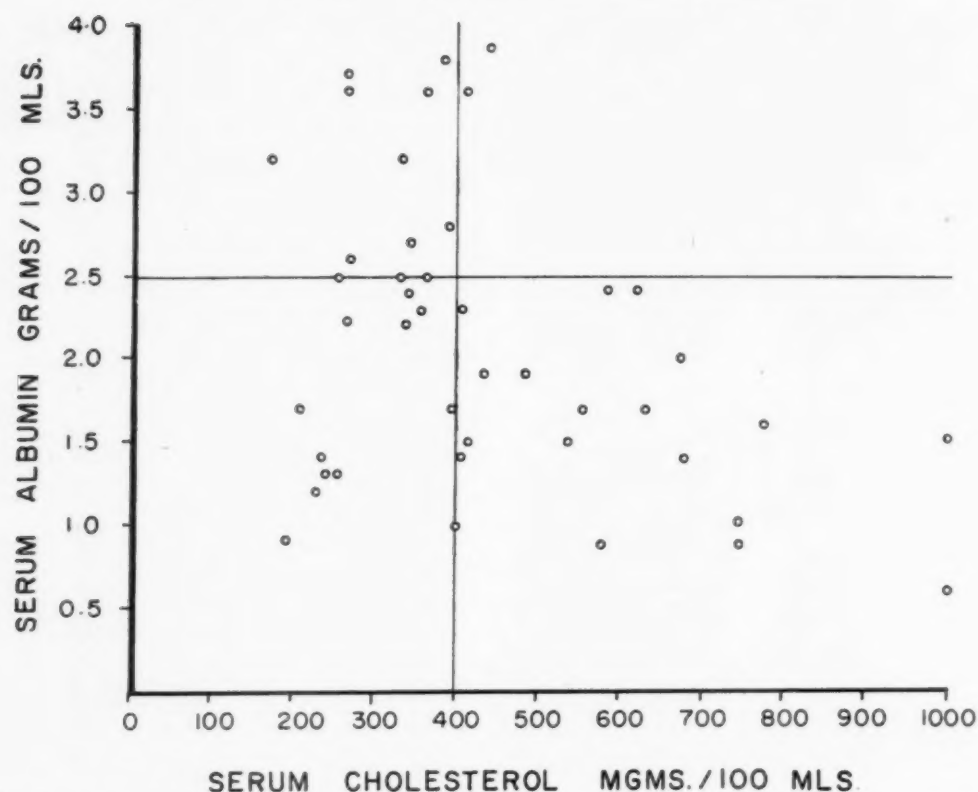


FIG. 21. Serum albumin concentration is plotted against serum cholesterol concentration with boundaries arbitrarily drawn at 2.5 gm./100 ml. and 400 mg./100 ml. Right upper quadrant emphasizes the rare occurrence of a markedly elevated cholesterol in the presence of a normal serum albumin. Note instances of normal cholesterol with low serum albumin concentrations. These were not related to any particular etiologic category.

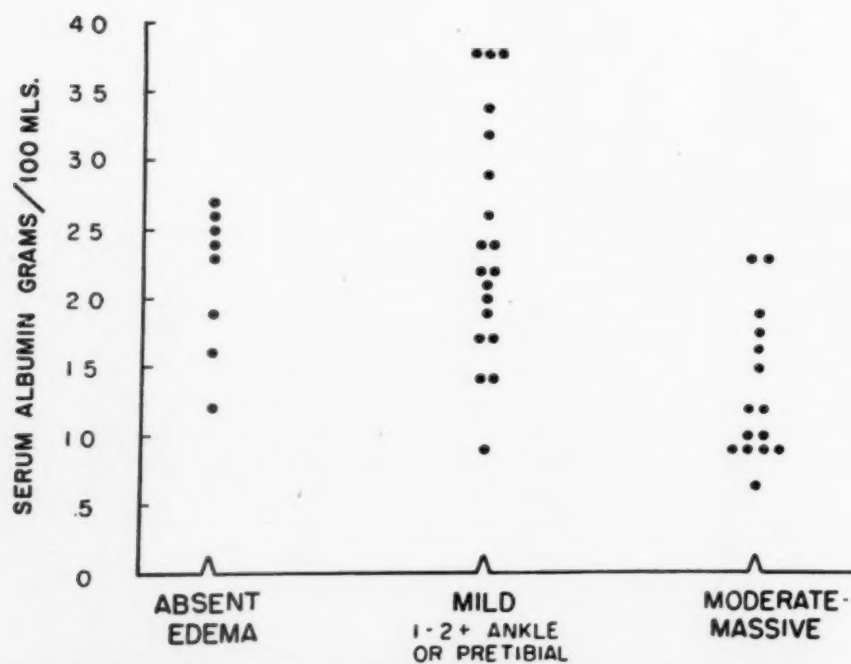


FIG. 22. Relationship of serum albumin concentration to edema in forty-one nephrotic patients.

variable and reflects the type and stage of the underlying disease. The presence of an elevated serum cholesterol concentration and a lowered serum albumin which has long been considered necessary to the diagnosis of nephrotic syndrome, was not found initially in 22 and 16 per cent, respectively, of our patients. These measurements, as well as the presence of edema have therefore been designated by the present authors as variable (although common) findings in the nephrotic syndrome. Patients who lack all three and show only gross proteinuria and lipiduria have been shown on biopsy to have the same kinds of pathologic changes that accompany the more classic syndromes. Furthermore, continued clinical observation has revealed the development of the one or more missing criteria in the course of time, thus providing sufficient justification for the definition of the nephrotic syndrome proposed in this paper.

Abnormal serum lipids have been used in the past to justify terming the nephrotic syndrome a metabolic disease. We have gradually tended to regard hyperlipemia as a secondary manifestation for the following reasons: Some patients do not have hyperlipemia until weeks or months after the development of other features of the nephrotic syndrome; elevated serum cholesterol is rare in the absence of hypoalbuminemia and usually increases with the degree of duration of proteinuria; patients with congestive failure or massive edema and normal serum cholesterol will tend to elevate their serum lipids following diuresis and lower them on reaccumulation of edema; we have not found significant cholesterol in nephrotic pleural, pericardial or ascitic fluid; heparin has slightly changed the fat pattern without affecting the clinical syndrome; and in nephrotic rats prevention of proteinuria inhibits the development of hyperlipemia. That the presumed transport defect may not always be reversible in man is suggested by the persistence of hyperlipemia in one of our patients through sixty days of anuria.

Following its introduction in 1951 [10] needle biopsy of the kidney has proved an indispensable tool in the development of newer concepts of renal disease. It is uniquely suited to investigation of the nephrotic syndrome, which is essentially a clinical "final common pathway" for a great variety of histologic alterations. The important question of glomerular basement membrane thickening, a source of despair to the pathologist who is limited to autopsy material, can be defi-

nately studied by means of biopsy specimens. The biopsy procedure itself was uneventful in the present series and permitted accurate diagnosis of atypical cases, early differentiation among multiple etiologic possibilities, and more exact estimate of the degree of glomerular involvement. Sick cell anemia and acute staphylococcal enteritis, two diseases hitherto unreported in association with a nephrotic syndrome, have had their accompanying glomerular alterations clearly delineated by means of renal biopsy.

The evaluation of therapy in the nephrotic syndrome has long suffered from lack of specific etiologic diagnosis in each case. It is clear that nephrotic patients cannot be simply assumed to have one or another etiology and then have their response to various therapies reported on that basis. Clinical thinking, which has so long been dominated by poststreptococcal glomerulonephritis in adults and a presumed "lipoid nephrosis" in children, must be broadened in accordance with the evidence reported here and in other biopsy series [51,52]. Meanwhile, significant data relating etiology to response to treatment is lacking. The present series, although too small for statistical analysis, suggests that a remission of the nephrotic syndrome with adrenocortical steroids may frequently be seen with membranous glomerulonephritis, the nephropathy of disseminated lupus erythematosus (excluding the stage of widespread glomerular destruction and azotemia) and selected cases of chronic glomerulonephritis, depending on the extent of glomerular destruction. Little or no data are available for the other categories of nephrotic patients, with the possible exception of the amyloidoses. These do not respond favorably to steroid therapy. The production of intercapillary glomerulosclerosis by steroids in alloxanized animals [53] argues for caution in any possible application of this therapy to human subjects with the nephrotic syndrome associated with Kimmelstiel-Wilson's disease.

The use of steroids in nephrotic syndromes of all etiologies is contraindicated when widespread, irreversible glomerular destruction has produced azotemia. Such patients may respond with rapid progression into uremia, hypertensive manifestations and death.

Finally, it may be useful to emphasize some difficulties which remain. Assuming that the nephrotic syndrome begins with, and depends upon, large and continued losses of albumin in the urine, the investigator's attention is im-

mediately engaged by the extraordinary variety of glomerular alterations associated with these losses. The problem is further complicated by the nephrotic patient whose biopsy reveals tubular disease with no definite glomerular pathology [54]. These observations may imply that all patients with the nephrotic syndrome have a common glomerular membrane defect which is independent of the glomerular pathology seen on conventional microscopy. Alternative explanations are possible: for example, certain nephrotic patients, perhaps those with normal appearing glomeruli, may lose protein through failure of tubular reabsorption of normally filtered protein. Final judgment must be withheld at present. Recourse to a hypothetical common renal functional defect in nephrotic patients merely begs the question of identifying the underlying structural defect, if we assume with Smith that, in a molecular world, structure always underlies function [55].

In the meantime, the clinician must exploit to the utmost the information which is presently available. Such information includes a steadily growing list of etiologies for the nephrotic syndrome, as well as its occurrence at almost any level of renal function, at various stages of the same disease, and with the widest possible variety of morphologic change in the kidneys. These facts make the nephrotic patient a highly individualized problem which does not lend itself to easy generalizations. Preoccupation with edema must never be allowed to interfere with an accurate etiologic diagnosis in every case, followed by a careful evaluation of renal function. Only in this way can rational prognosis and therapy be achieved.

SUMMARY

1. The nephrotic syndrome is defined as a clinical state characterized by excretion into the urine of 3.5 or more gm. of protein per day, together with doubly refractile or oval fat bodies. There is a variable tendency toward edema, hypoproteinemia and hyperlipemia, possibly dependent on the amount and duration of protein loss.

2. Clinical and laboratory studies on forty-nine patients with a nephrotic syndrome are correlated with thirty-six renal biopsies and nine autopsies.

3. The histologic classification of the forty-five nephrotic patients is divided into eight categories: membranous glomerulonephritis (ten

patients), acute and chronic glomerulonephritis (twenty-one), intercapillary glomerulosclerosis (three), amyloid disease (four), disseminated lupus erythematosus (four), sickle cell disease (one), interstitial nephritis with a diffuse and local membranous glomerulonephritis (one) and probable renal vein thrombosis (one).

4. Correlation of clinical and laboratory findings with renal histology has been found necessary, not only in research but also for the proper diagnosis and treatment of the patient.

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Seminar on Liver Disease

Chronic Idiopathic Jaundice*

A Review of Fifty Cases

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RECENTLY a new hepatic disease was described independently by two sets of workers, namely, Dubin and Johnson [1,2,3], and Sprinz and Nelson [4], under the terms "chronic idiopathic jaundice with unidentified pigment in liver cells" and "persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells," respectively. The disease manifests itself as a form of chronic or intermittent jaundice in young people. The commonest clinical findings are abdominal pain, fatigue, dark urine and slight hepatomegaly. The jaundice fluctuates in intensity and is aggravated by intercurrent diseases. The disease may be lifelong, and the prognosis is excellent. Since the original descriptions, new data have become available which have increased our knowledge of the disease: additional cases have come to light, and follow-up data on the original patients have been collected. This later material has sharpened the outlines of some aspects of the disease which heretofore were only nebulous, although hinted at in the original observations. It is the purpose of this paper to review all known cases in order to delineate our current knowledge of the subject.

FOLLOW-UP DATA ON THE ORIGINAL CASES

Twelve cases were described in our original report [2]; follow-up data, covering the period from 1953 to 1956, were obtained in all but one.

CASE 1. AFIP Accession 148686. A white man, now aged thirty-nine, reported in March 1956 that since July 1953 his condition has remained unchanged. He still suffers from chronic jaundice, fatigue and pain in the right side of the abdomen.

CASE 2. AFIP Accession 266673. A white man, now aged thirty-three, reported in March 1956 that

since February 1953 he has had "bilious attacks" characterized by severe headache and heaving of bile. He has had no jaundice.

CASE 3. AFIP Accession 312366. A white man, now aged twenty-five, reported in March 1956 that since April 1953 he has continued to suffer from jaundice and pain in the right side of the abdomen.

CASE 4. AFIP Accession 520257. In the original article [2] the last report was dated December 1952 at which time this patient was discharged from the U. S. Army. He next was admitted to the Veterans Administration Hospital, Los Angeles, California on November 5, 1954, where he was studied by Dr. James Halstead and Dr. Vernon Liberman [5]. This twenty-four year old white man complained of jaundice which appeared November 3, 1954, two days after extraction of impacted teeth. Between December 1952 and November 1954, he had had about forty episodes of cramping pain in the right upper quadrant of the abdomen, associated with weakness but no jaundice. On physical examination the only abnormality noted was jaundice of the sclerae. The gallbladder did not visualize with a double dose of oral dye. The urine was dark amber and contained bile, but the twenty-four-hour urinary urobilinogen was normal (3.1 mg.). The serum bilirubin was: direct 2.9 mg., total 3.1 mg. per cent. Results of other tests were as follows: bromsulphalein retention, 19 per cent; prothrombin time, normal; alkaline phosphatase 2.9 units; cephalin flocculation test, negative; thymol turbidity test, 4 units. On November 10, 1954, a needle biopsy of the liver was performed and the fresh tissue so obtained was almost black. Histologically, the liver was normal except for intense pigmentation of parenchymal cells, as was seen in earlier biopsy specimens. The physicians quickly recognized that the patient was one of those reported in our original series; he was discharged from the hospital on November 17, 1954, and returned to work as a service station operator. He was studied further in the out-patient clinic by Dr. Marvin

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Gasster [6] who reported in April 1955 that the gallbladder still failed to visualize after intravenously administered cholografin.

CASE 5. AFIP Accession 528670. This twenty-five year old white man reported in April 1955 that since January 1953 he still suffered from jaundice, weakness and pain in the region of the liver. The symptoms seemed to come on after hard physical work.

CASE 6. AFIP Accession 534280. This twenty-three year old white man reported in April 1956 that since March 1953 he still had episodes of weakness and pain in the right side and that jaundice recurred every few months.

CASE 7. AFIP Accession 547327. In the earlier paper [2] we reported that an exploratory laparotomy was performed on September 5, 1952, because cholelithiasis was suspected. However, no calculi were found. The patient was discharged from the hospital on January 10, 1953.

In March 1954, the patient (now aged forty-four) reported that he still suffered from jaundice, nervousness and fatigue. He returned to the Veterans Administration Hospital in Louisville, Kentucky for further study on April 25, 1955 [7]. At that time he was jaundiced and anxious. The liver was felt 2 fingerbreadths below the costal margin but was not tender; the spleen was not palpable. On admission the serum bilirubin was 2.0/2.5 mg. per cent; alkaline phosphatase, 2.8 Bodansky units; bromsulphalein retention, 17 per cent. The following studies gave normal results: urinalysis, prothrombin time, cephalin flocculation test, fecal and urinary urobilinogen, Coombs' test, serum proteins, non-protein nitrogen and blood glucose. On April 28 he experienced severe cramping abdominal pain in the right upper quadrant. Cholecystography with intravenous cholografin on April 29 resulted in a diagnosis of multiple radiolucent stones in the gallbladder; but on May 4 the gallbladder did not visualize on oral cholecystography, using telepaque. On May 9, 1955, a cholecystectomy was performed; the gallbladder contained many small calculi and showed evidence of chronic inflammation on histologic study. A liver biopsy specimen taken at this time showed the identical pigmentation of liver cells that had been present in the specimen obtained three years earlier. There was no change in the histologic picture except for a mild degree of inflammation of portal areas, which was probably secondary to the chronic cholecystitis.

Shortly after operation, jaundice deepened and anorexia and vomiting appeared. This episode lasted five days after which the symptoms disappeared and jaundice abated quickly. On May 12 the serum bilirubin was 13 mg. per cent; alkaline phosphatase, 4.3 units; and cephalin flocculation test, negative. On May 16 the serum bilirubin was 8.6 mg. per cent;

alkaline phosphatase, 6.9 units; and two-hour urine urobilinogen, 2.7 Ehrlich units. On May 19 a cholangiogram was normal and the T tube was removed. On May 23, the day before discharge from the hospital, his serum bilirubin was 4.6 mg. per cent. In March 1956 the patient reported that he was still weak and slightly jaundiced.

CASE 8. AFIP Accession 559853. This case was reported independently by Sprinz and Nelson [4] as their Case II. The patient, a twenty-six year old white man was discharged from the Army in January 1953. In March 1956 he wrote that he still had pain in the region of the liver and was often tired and listless; he was free of jaundice.

CASE 9. Accession 565140. No additional information was obtained.

CASE 10. Accession 572652. This case was reported independently by Sprinz and Nelson [4] as Case I in their series. The patient left the hospital on November 14, 1952. In April 1953 she wrote us that her eyes were still yellow.

In April 1956 (now aged forty-six) she reported that she continued to suffer from jaundice, diarrhea, fatigue and nervousness. At the same time we heard from the physician who had attended her at an Army Hospital; evidently he had not been notified of her true condition because the patient was being treated for "cirrhosis resulting from chronic infective hepatitis." In February 1956 the patient was described as a chronically ill, slightly jaundiced woman, with a tender but non-palpable liver. Laboratory studies gave the following results: serum bilirubin, 2.4 mg. per cent; prothrombin time, 100 per cent; cholesterol, 235 mg. per cent with esters 79 per cent; cephalin flocculation test, negative; thymol turbidity test, 4.4 units; bromsulphalein retention, 11 per cent; blood counts and urinalysis, normal. Her attending physician was immediately apprised of the correct diagnosis.

CASE 11. AFIP Accession 574403. This twenty-four year old Puerto Rican man was originally studied at Brooke Army Hospital by Col. B. H. Sullivan, who sent me liver biopsy specimens for pathologic diagnosis. On recognizing the disease entity, I advised against an exploratory laparotomy and the patient was returned to duty on April 20, 1953. He was well until June 2, 1953, when he was admitted to the Army Hospital at Camp Kilmer, New Jersey, complaining of anorexia, jaundice and pain in the region of the liver. The total serum bilirubin was 3.7 mg. per cent; thymol turbidity test, 16.3 units; alkaline phosphatase, 2.6 units; and cephalin flocculation test, 3 plus. Next day his rectal temperature rose to 107°F. and malarial parasites were found in the blood. His fever responded quickly to chloroquine therapy. He became asymptomatic in two or three days but his total serum bili-

rubin stayed at 2 mg. per cent. Because of his persistent hyperbilirubinemia he was transferred to Walter Reed Army Hospital on August 13, 1953, where he was studied by Col. H. Sprinz and others; his case report appears as Case iv in their series [4]. The serum bilirubin was 0.93/1.7 mg. per cent on admission but later rose as high as 1.6/3.5 mg. per cent. Other liver function tests gave normal values. The urine contained a trace of bile. The erythrocyte fragility was normal and the Coombs' tests was negative. Red cell survival studies with chromated red cells showed a normal life span. The excretion of fecal and urinary urobilinogen was normal. The twenty-four hour excretion of urinary coproporphyrin ranged between 244 and 694 μ g. The gallbladder again failed to visualize on cholecystography. Another needle biopsy specimen of liver was obtained on October 30, 1953; the appearance was identical with that of the specimens obtained in December 1952 and March 1953.

CASE 12. AFIP Accession 579414. This twenty-four year old white man was discharged from Brooke Army Hospital in June 1953. In April 1955 he wrote that he still suffered from jaundice. In March 1956 his physician reported that the patient was slightly jaundiced and that the total serum bilirubin was 2.95 mg. per cent and the thymol turbidity test was 1.2 units.

ELEVEN NEW CASES IN REGISTRY OF HEPATIC PATHOLOGY

After the original report, I studied eleven new cases in the Registry of Hepatic Pathology.

CASE 13. AFIP Accession 595499. This patient was reported by Sprinz and Nelson [4] as Case iii in their series. I saw this patient at Walter Reed Army Hospital through the courtesy of Col. Sprinz.

This twenty-two year old white man was admitted to the hospital on June 22, 1953, complaining of intermittent jaundice of five years' duration. There was no history of jaundice in the family. The most recent episode of jaundice began on March 17, 1953, two days after onset of sore throat, fever and chills; these symptoms subsided quickly after penicillin therapy, but the jaundice persisted. He was treated for "acute hepatitis" in an Army Hospital in Korea and also in Japan. On admission to Walter Reed Army Hospital he had slight icterus and complained of mild nausea and epigastric discomfort. On several occasions the serum bilirubin was approximately 2.0/3.2 mg. per cent. The urinary urobilinogen excretion was increased in March but was normal thereafter. The fecal urobilinogen was normal. Bromsulphalein retention ranged from 10 to 17 per cent. The thymol turbidity test was 8 units in March 1953 but returned to normal levels. Other liver function tests gave normal values. The erythrocyte fragility was normal. The gallbladder twice failed to visualize on cholecystog-

raphy. A needle biopsy specimen of liver was obtained on June 30, 1953; the liver was normal except for a marked degree of pigmentation of parenchymal cells. A bone marrow aspirate showed an occasional deposit of pigment granules in reticulum cells which were considered by Col. Sprinz to be similar to the pigment in the liver. Biopsy specimens of skin, muscle, fat, gastric mucosa and rectal mucosa were normal and free of pigment. The patient's symptoms disappeared and he returned to military duty in August 1953.

He wrote us in March 1956 that he felt well but that his eyes were still jaundiced.

CASE 14. Accession 631520. A nineteen year old white man, a French national serving in the French Navy, was admitted to a U. S. Naval Hospital in Japan in September 1953 complaining of intermittent abdominal pain and jaundice of seven years' duration. The urine contained an increased amount of urobilinogen. A needle biopsy specimen of liver was obtained on October 20, 1953. The liver showed pigmentation of parenchymal cells in the central zones. The pathologist's diagnosis was "virtually normal liver tissue." Sections were submitted to the Armed Forces Institute of Pathology where the true nature of the disease was recognized.

The remainder of this case report was recently obtained from the clinical records of a French military hospital. Apparently, our diagnosis had not reached the physicians in this institution. The patient was admitted to a hospital in Saigon, Indochina on January 26, 1954, complaining of jaundice and pain in the right hypochondrium; during the hospital stay, mild jaundice and dark urine were noted. A diagnosis of hemolytic jaundice was made, and the patient was sent to the country for a vacation. He was readmitted to the hospital on March 31, 1954, saying that he had had another episode of abdominal pain one month before. On physical examination slight jaundice was noted. The liver and spleen were not palpable. The urine was dark. Cholecystography on June 22 displayed the gallbladder. He was discharged on July 6, 1954, with a diagnosis of hemolytic jaundice. He was again seen in the hospital on July 29 because of nausea and abdominal pain, and was readmitted to the hospital on October 18, 1954, for further study. Complete blood count, reticulocyte count, erythrocyte fragility, and tests for autoantibodies gave normal values. The serum bilirubin was 3.4 mg. per cent, with a direct van den Bergh reaction. The urine contained bile pigments. The blood cholesterol was 225 mg. per cent; thymol turbidity reaction, 5 units cephalin flocculation test, negative; Takata test, 2 plus; Kunkel zinc test, 8 units. The patient was discharged from the service in December 1954 with partial disability granted.

CASE 15. AFIP Accession 636071. A twenty-one year old white man was admitted to Madigan Army

Hospital in February 1954 because of persistent jaundice. His family history was noteworthy in that his mother was jaundiced in childhood and also in later life. The patient's first episode of jaundice, lasting two weeks, occurred in July 1951 at the age of eighteen. After recovering from this attack he remained well until August 7, 1953, when he noted anorexia, nausea, fatigue, pain in the region of the liver, jaundice and dark urine. At that time he was studied in two U. S. Army Hospitals in Germany over a period of twenty weeks. Except for mild jaundice no abnormalities were found on physical examination. The total serum bilirubin ranged between 2.1 and 2.9 mg. per cent. Other liver function tests gave normal values. He was transferred to Madigan Army Hospital, where he was studied from February to May 1954. His serum bilirubin ranged from 0.7/1.2 to 1.7/3.3 mg. per cent, and bromsulphalein retention from 7 to 17.5 per cent. The following additional tests were made: all of which gave normal results: cephalin flocculation, thymol turbidity, serum alkaline phosphatase, serum cholesterol, serum proteins, heterophil agglutinins, urine urobilinogen, fecal urobilinogen, reticulocyte count, Coombs' test, and glucose tolerance. A needle biopsy specimen of liver was obtained on February 25, 1954. The liver showed the typical pigmentation of parenchymal cells but was otherwise normal histologically.

The patient was then studied in Walter Reed Army Hospital from June 5 to September 2, 1954. There was a moderate degree of scleral icterus and the liver was felt 2 fingerbreadths below the costal margin. The complete blood count, reticulocyte count, erythrocyte fragility, and erythrocyte survival time with chromium⁵¹ were within normal limits. The bleeding, coagulation and prothrombin times were normal. There was no bile in the urine; but levels of urinary urobilinogen fluctuated between normal and increased amounts (e.g., 8.0 mg. per day). The fecal urobilinogen was normal in amount. The serum bilirubin ranged from 1.3/2.8 to 1.7/3.8 mg. per cent. Bromsulphalein retention was 15 per cent on two occasions. The following tests gave normal results: cephalin flocculation, thymol turbidity, zinc turbidity, serum alkaline phosphatase, serum proteins, serum cholesterol and blood urea. The gallbladder twice failed to visualize on cholecystography. ACTH caused no significant change in serum bilirubin or in excretion of fecal and urinary urobilinogen; 40 units of ACTH was given twice daily for four days; this was preceded and followed by eight-day control periods. A needle biopsy specimen of liver was obtained on June 9, 1954. The fresh specimen was black. It was identical histologically with the one taken in February 1954. The disease was recognized and the patient was discharged with a good prognosis. In March 1956, the patient wrote that he had no jaundice but was troubled occasionally with fatigue and anorexia.

CASE 16. AFIP Accession 650889. This twenty-five year old white woman was studied at the U. S.

Army Hospital, Fort Knox, Kentucky from February 24 to March 18, 1954 by Col. Robert S. Nelson who has reported the case in detail elsewhere [8]. There was no history of jaundice in the family. The patient was jaundiced for three days at birth but remained well until the age of fourteen, when she noted dark urine, anorexia, nausea, pain in the right upper quadrant of the abdomen, light stools and jaundice; her physician told her that she had a "big liver." She had similar episodes at age sixteen and nineteen, respectively, each lasting about six weeks. During the intervals her eyes remained slightly yellow.

On admission to the hospital she was well except for slight jaundice. She was four months pregnant. The liver was felt 3 fingerbreadths below the costal margin, and was tender. Except for anemia, the complete blood count was normal. The urinalysis was negative, but no tests were made for bile or urobilinogen. The reticulocyte count, erythrocyte fragility and Coombs' test gave normal results. The serum bilirubin ranged from 1.7/2.35 to 2.15/2.85 mg. per cent. The cephalin flocculation test was 2 plus; the thymol turbidity test was 6.5 units; and bromsulphalein retention was 15 per cent. The following tests gave normal values: prothrombin time, serum cholesterol, blood glucose and serum alkaline phosphatase.

A needle biopsy specimen was obtained on March 2, 1954. The fresh specimen was very dark and Col. Nelson suspected the true nature of the disease at that time. Histologic examination showed a normal liver except for pigmentation of the parenchymal cells. The pathologist mistook the pigment for bilirubin but when the case was submitted to us at the Armed Forces Institute of Pathology we confirmed Col. Nelson's diagnosis. Histochemical tests carried out at this time by Dr. F. B. Johnson gave results identical with those reported in our first paper. The patient was discharged from the hospital on March 18, 1954, and Col. Nelson informed the obstetrician that the patient's prognosis was good.

Jaundice increased just before delivery. On July 29 the serum bilirubin was 5.4/7.4 mg. per cent, the thymol turbidity test was 5 units, and the cephalin flocculation test was 4 plus. Following delivery the serum bilirubin dropped to previous levels. In February 1955 the serum bilirubin was 2.1/3.0 mg. per cent; thymol turbidity test, 6 units, cephalin flocculation test, 3 plus, and bromsulphalein retention, 5 per cent. The baby (a boy) was completely well and free of jaundice; his serum bilirubin in February 1955 was 0.2/0.6 mg. per cent. In March 1956 the patient wrote us that she was perfectly well and had had no further trouble since the early part of 1955.

CASE 17. AFIP Accession 677482. This case was submitted by Dr. A. Askireli [9] of the Rambam Government Hospital, Haifa, Israel; Dr. Askireli plans to publish a detailed case report later.

The patient was a twenty-five year old white man

who had lived in Israel for five years; he was born in Persia of Persian-Jewish parents. One brother living in Persia, had recurrent jaundice. The patient had had an attack of jaundice at the age of one year and again at age eighteen; following this his jaundice became less severe but never disappeared. At age twenty-one he was admitted to the Rambam Hospital for the first time, complaining of weakness and pain in the upper part of the abdomen. The liver was slightly enlarged; the spleen was not palpable. The total serum bilirubin was 2.9 mg. per cent; the direct reaction was positive. The prothrombin time was 32 per cent, but reached 100 per cent after administration of vitamin K. Other liver function tests were normal. The gallbladder did not visualize on cholecystography. Two exploratory laparotomies were performed that year: the liver was enlarged and dark, and the biliary tract was normal. Between 1950 and 1954 several needle biopsy specimens of liver were obtained; the specimen submitted by Dr. Askireli was taken in 1952; the liver showed the characteristic pigmentation of parenchymal cells but was otherwise normal. During the four years that the patient was studied there was no change either in the clinical picture or in the histological appearance of the liver.

CASE 18. AFIP Accession 681569. This case was submitted by Dr. Andrew Ranier [10] of St. Patrick's Hospital, Lake Charles, Louisiana. Dr. Ranier will publish a detailed case report later.

A thirty-one year old white woman was admitted to the hospital on April 15, 1949, in the ninth month of her second pregnancy, because of jaundice and dark urine. She was well until November 1948 when acute bronchitis developed, manifested by fever, general malaise and a productive cough. This was followed by otitis media a month later. These ailments subsided for a short time only to recur in January 1949. The patient's condition improved somewhat after penicillin therapy but cough persisted. Jaundice was first noted in March 1949. At that time the icteric index was 5 and the urine contained no bile or increased urobilinogen. In April jaundice deepened and the patient noted pain in the right upper quadrant of the abdomen; the urine contained bile. She was then admitted to the hospital.

On physical examination the patient, who was near term, showed slight jaundice as the only abnormal sign. There was no history of jaundice in the family. From April 15 to April 27 the icteric index varied from 12 to 25 units. The van den Bergh test showed a direct reaction. Bile was found in the urine every day, but not increased urobilinogen. The hemoglobin was 70 per cent; erythrocyte fragility was normal. The prothrombin time was 80 per cent. The serum cholesterol was 270 and 202 mg. per cent, respectively, on two tests. It was believed that the patient had definite hepatic damage, and labor was induced with pitocin.[®] She gave birth to a normal baby

girl and was discharged from the hospital on April 27, 1949. During the remainder of 1949 her icteric index ranged from 15 to 20 units and bile was found in the urine of three of four specimens. In 1950 the icteric index remained at about 10 units and bile was found in the urine only once; the cephalin flocculation test was 2 plus. In 1951 bile was again found in the urine; the icteric index was 15. In 1954 the cephalin flocculation test was 4 plus. The patient was again admitted to the hospital on October 20, 1954, complaining of periodic episodes of jaundice and a dull, aching abdominal pain in the "gallbladder region." X-ray studies suggested gallstones. On the day of admission to the hospital the hemoglobin was 12.5 gm. and the urine contained a trace of bile. She was operated upon on the following day. The liver was enlarged and darkly pigmented. There was no evidence of biliary obstruction; the pancreas, gallbladder and bile ducts were normal, and no gallstones were found. A specimen of liver and the sentinel node of the gallbladder were removed for study. Histologically the liver was normal except for marked pigmentation of the parenchymal cells. The lymph node also contained a brown pigment which Dr. Ranier believed similar to the one in the liver. He recognized the disease entity and sent us the biopsy specimen of the liver. During her hospital stay the following laboratory results were obtained: total serum bilirubin, 4.15 mg. per cent, with a direct reaction; bromsulphalein retention, 20 per cent; prothrombin time, 41 per cent; bile and increased urobilinogen in the urine; erythrocyte fragility, normal, and Coombs' test, negative. The patient was discharged from the hospital eight days after admission. Two weeks later laboratory studies gave the following results: serum bilirubin, 0.6 mg. per cent; prothrombin time, 90 per cent; bromsulphalein retention, none; cephalin flocculation test, negative; thymol turbidity test, 8 units; bile and increased urobilinogen in urine; serum proteins and blood glucose, normal. Dr. Ranier followed up the patient and reported in April 1956 that she still complained of recurrent jaundice, and pain in the right upper quadrant of the abdomen.

CASE 19. AFIP Accession 694877. This case was studied by Drs. Wade Volwiler [17], G. G. John and K. P. Knudtson of the Veterans Administration Hospital, Seattle, Washington. John and Knudtson recently published a report of this case and that of the patient's sister, who also had the disease [12].

A white man, aged nineteen, had been well until January 1945 when he participated in the Battle of the Ardennes. He experienced weakness two days prior to the battle, and after five days of great physical strain on battle duty, noted anorexia, dark urine, light stools and abdominal pain in the right upper quadrant. He went on sick call January 8, 1945, when jaundice was noted. He was admitted to a hospital in England on January 15, 1945, where he was

treated for "chronic hepatitis" during the next three months. During this time the degree of jaundice fluctuated and was accompanied by abdominal pain when jaundice was at its height. The icteric index varied from 10 to 24, but the hippuric acid test, serum proteins and erythrocyte fragility were normal. The gallbladder did not visualize on cholecystography. In April 1945 he was transferred to the United States and remained in the hospital until October 4, 1945, when he was discharged from the military service with a diagnosis of "chronic infectious hepatitis." During this period bile was occasionally present in the urine, but urinary urobilinogen was normal. The icteric index ranged between 18 and 28. Bromsulphalein retention was 4, 28 and 8 per cent, respectively, on three tests. The erythrocyte fragility was normal. The gallbladder again failed to visualize on oral cholecystography. He continued to have frequent episodes of jaundice, fatigue, anorexia, abdominal pain and dark urine. In June 1947 he was studied at the Crile Veterans Administration Hospital where the following data were obtained: serum bilirubin, 3.2 mg. per cent; thymol turbidity test, 9.8 units; serum cholesterol, 150, and no retention of bromsulphalein. His attacks continued, sometimes precipitated by unusual physical activity. On December 22, 1954, he had a severe, steady pain in the epigastrium. This was followed a few days later by dark urine, jaundice and light watery stools. Studies in the clinic showed hyperbilirubinemia and a non-visualizing gallbladder. He entered the Veterans Administration Hospital in Seattle on January 26, 1955. There was no history of jaundice in the parents or in four siblings, but one sister, aged thirty-three, had a history of recurrent jaundice since the age of twelve. On physical examination he showed mild jaundice and tenderness to percussion in the area of the liver. The urine contained bile. The serum bilirubin was 2.0/4.2 mg. per cent. The following tests gave normal values: complete blood count, cephalin flocculation, prothrombin time, thymol turbidity, serum alkaline phosphatase, bromsulphalein retention, serum proteins, serum amylase, serum cholesterol and two-hour urine urobilinogen. The gallbladder visualized only faintly after a double dose of oral dye. An exploratory laparotomy was performed on February 9, 1955. The liver was slightly enlarged, smooth and purplish blue. The pancreas, gallbladder and bile ducts were normal. A specimen of liver and a periduodenal lymph node were taken for study. The following day the serum bilirubin was 6.5 mg. per cent; serum alkaline phosphatase, 1.5; thymol turbidity test, 0.3 and bromsulphalein retention, 18 per cent. Histologically, the lymph node showed only reactive hyperplasia. The liver showed the typical pigmentation of liver cells, but was otherwise normal. The diagnosis of "chronic idiopathic jaundice with pigmented liver" was made and was confirmed by us. After an uneventful postoperative course the patient was discharged

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on February 24, 1955. He returned to work but jaundice was still present.

The patient's sister, who had recurrent jaundice, was studied further and was found to have the same disease, confirmed by liver biopsy. This case will be discussed later.

CASE 20. AFIP Accession 707068. This case was submitted by Professor J. H. Dible [13], Postgraduate Medical School, London, England.

The patient, a white boy aged four years and one month, was admitted to the Royal Berkshire Hospital, Reading, England on February 2, 1955. He was the fifth child. The first two children, aged fourteen and ten, were normal. The third child died at three weeks and had been jaundiced soon after birth. The fourth child was jaundiced at birth but was normal thereafter. The patient himself was first seen at age two months because of "pallor," but no apparent disease was found.

He was admitted to the hospital with a forty-eight hour history of abdominal pain and vomiting. Blood was passed per rectum. On physical examination a mass was felt in the right side of the abdomen, and mild jaundice was noted. The child was extremely ill and died while an intravenous drip was being set up. The autopsy was performed by Dr. J. H. Mills [13] who found gangrenous ileocecal intussusception. An incidental finding was dark pigmentation of the liver. No other abnormalities were found grossly. After histologic study Dr. Mills considered the possibility that the pigment in the liver cells might be melanin and sent the sections to Professor Dible. Histologically the liver was normal except for pigmentation of parenchymal cells in centrilobular zones. Professor Dible recognized the condition and sent me the histologic material. The pigment had the same histochemical properties previously described.

CASE 21. AFIP Accession 713707. A twenty-one year old white man was admitted to a U. S. Army Hospital in Germany in 1954 because of recurrent jaundice. He had been jaundiced in 1944 (age eleven), but without associated symptoms. He had been refused enlistment in the Air Force in 1953 because of jaundice. On physical examination the only abnormalities noted were jaundice and a palpable liver and spleen. During the hospital stay he was asymptomatic. The complete blood count and reticulocyte count were normal. Bone marrow studies showed no evidence of hemolytic disease; the Coombs' test was negative. There was no bile or increased urobilinogen in the urine. The liver profile was normal except for a serum bilirubin of 1.28/2.58 mg. per cent. A needle biopsy specimen of liver was obtained in June 1954. Pigmentation of the parenchymal and Kupffer cells was noted and the pathologist made a diagnosis of "liver showing pigmentation, type undetermined." The case was reviewed and correctly

diagnosed by Maj. Edwin E. Pontius [14] at the Landstuhl Army Medical Laboratory, Germany and was confirmed by Dr. Leo Krainer [15] of the Armed Forces Institute of Pathology. The histochemical properties were the same as in other cases previously reported. In this case the pigment was not sharply restricted to the centrilobular zones but was more diffusely scattered; some pigmentation also occurred in Kupffer cells. Other histologic changes were minimal, comprising minimal fatty metamorphosis, slight inflammation of portal areas, prominence of Kupffer cells and vacuolization of liver cell nuclei.

In April 1956 the patient reported he was perfectly well.

CASE 22. AFIP Accession 714324. This patient was studied by Dr. J. Richmond Low and Dr. Geoffrey T. Mann [16] at the Mary Washington Hospital in Fredericksburg, Virginia.

A thirty year old white woman came to the hospital in June 1955 complaining of jaundice and pain in the right upper quadrant of the abdomen. The family history was negative. The patient's illness had begun insidiously nine years earlier, immediately after the birth of her only child, who is apparently normal. She had received no blood transfusions. In the postpartum period, jaundice, lethargy and general malaise appeared. Since then she has had slight jaundice, varying in intensity, but constantly present. For six months prior to this hospital admission she had had frequent attacks of heartburn, abdominal pain in the right upper quadrant, and dark urine. On physical examination the only abnormalities found were jaundice and tenderness in the right upper quadrant of the abdomen. The serum bilirubin was 2.4/2.8 mg. per cent; icteric index, 19; serum alkaline phosphatase, 2.8; cephalin flocculation test, negative; and serological reactions, negative. The urine did not contain bile or increased urobilinogen. The gallbladder did not visualize on cholecystography. An exploratory laparotomy was performed. The liver resembled dark mahogany in color; it was small and had a thick capsule. The gallbladder and bile ducts were grossly normal and a cholangiogram was also normal. A specimen of liver was taken for histologic study. There was pigmentation of the parenchymal cells and mild portal scarring and round cell infiltration; stains for iron and bilirubin gave negative results; the pigment was bleached slightly by hydrogen peroxide. Dr. Mann recognized the disease entity and sent the case to the Armed Forces Institute of Pathology where the diagnosis was confirmed by Dr. Leo Krainer [15]. In March 1956 Dr. Low stated that the patient had been entirely well since she left the hospital in 1955.

CASE 23. AFIP Accession 735385. This case was studied by Dr. J. S. Margulies and Dr. Donald H. Finger [17], who plan to publish a detailed case report later.

A twenty year old white man was admitted to the

hospital at Fort Francis E. Warren Air Force Base in 1955 because of recurrent jaundice of several years' duration. The family history was negative. The patient had an attack of painless jaundice in August 1955 and was treated for "infectious hepatitis." The jaundice recurred a month later. From October 18 to December 9, 1955, the following data were obtained: the serum bilirubin ranged from 1.1/1.4 to 1.8/2.4 mg. per cent and the icteric index from 16.4 to 26; cephalin flocculation test, thymol turbidity test, serum alkaline phosphatase, serum proteins and serum cholesterol were normal. Repeated studies for hemolysis gave negative results; these included complete blood count, bone marrow aspiration, reticulocyte count, erythrocyte fragility, Coombs' test, and fecal and urinary urobilinogen. Cholecystography on two occasions failed to display the gallbladder. A needle biopsy specimen of liver was obtained early in December; the liver was normal except for pigmentation of parenchymal cells. The pathologist believed the process was due to some hemolytic disease.

An exploratory laparotomy was performed on December 22, 1955. No evidence of biliary obstruction was found; the cholangiogram was normal. The liver was smooth and slightly green. The spleen was thought to be somewhat enlarged, and was excised. Biopsy specimens from the right and left lobes of the liver and a hilar lymph node were also excised for study. The liver showed centrilobular pigmentation of the parenchymal cells but was otherwise normal. The spleen weighed 265 gm. and was somewhat congested. There were no significant histologic changes in the spleen or lymph node; in particular, no pigment was found. The pathologist made a diagnosis of "hepatitis, etiology undetermined" and sent the patient in consultation to the Armed Forces Institute of Pathology where the correct diagnosis was made by Dr. Leo Krainer [15]. Histochemical properties of the pigment were identical with those previously reported. After operation the serum bilirubin rose: on December 31, the icteric index was 30 and the serum bilirubin was 2.3/3.0 mg. per cent; by January 9, 1956, it had fallen to 1.9/2.1 mg. per cent. The patient went on leave and when he was studied again on February 7, 1956, he was well and free of jaundice.

REVIEW OF OTHER PUBLISHED CASES

Klajman and Efrati [18] reported a case from Israel. A twenty-eight year old white woman was studied in June 1954 because of recurrent jaundice and epigastric pain since 1948. The most recent episode of jaundice was precipitated by pregnancy. Jaundice and a palpable liver comprised the only abnormal physical signs. The serum bilirubin was 1.8/3.0 mg. per cent; thymol turbidity test, 6 units; other liver function tests gave normal values. The urine contained bile and increased urobilinogen. The fecal urobilinogen was normal. Complete blood count, erythrocyte fragility and Coombs' test gave normal

results. The gallbladder failed to visualize on cholecystography. She was delivered in October, 1954, of a child that died soon after, of causes unknown. She was readmitted to the hospital a month later, still jaundiced, with a serum bilirubin of 3.6/4.8 mg. per cent, thymol turbidity test, 5 units, bromsulphalein retention, 28 per cent; and a non-visualizing gallbladder. A needle biopsy specimen of liver showed pigmentation of the parenchymal cells. She was studied again in the hospital in January 1955 at which time the laboratory studies and liver biopsy elicited findings identical with those in November. An exploratory laparotomy was being considered by the physicians but was abandoned as unnecessary because at this point they came across our original report [2]. The patient has continued in excellent general health apart from jaundice.

Castleman [19] reported the case of a fifteen year old white girl who was admitted to the Massachusetts General Hospital in 1951 because of recurrent attacks of "liver trouble." One brother had had jaundice four years previously. The girl's jaundice was first noted seven months earlier, during an episode of infectious mononucleosis; at that time the urine was dark and the icteric index 15 units. Jaundice persisted, and several months later she had to leave school because of her illness; at this time her liver was tender and slightly enlarged; the icteric index was 20 units; the cephalin flocculation test was 3 plus; and the urine was free of bile. A similar episode occurred shortly after, marked by fatigue, abdominal cramps and jaundice.

On admission to the hospital in 1951, the girl looked well except for questionable scleral icterus. A palpable liver and spleen were noted. The serum bilirubin was 1.9/2.7 mg. per cent; cephalin flocculation test, 2 plus; serum iron, 330 μ g. per cent. Other laboratory studies gave normal values. The gallbladder did not visualize on cholecystography. A needle biopsy specimen of liver was obtained. Dr. T. B. Mallory described a normal liver except for pigmentation of parenchymal cells. Special stains ruled out hemosiderin, ceroid, hematoïdin, lead and bismuth. A definite diagnosis was not made.

She was readmitted to the Massachusetts General Hospital three and a half years later. After her discharge from the hospital in 1951 she had felt well but the serum bilirubin had remained elevated. Jaundice had been temporarily aggravated by an attack of "grippe" and by an arthrotomy of the knee. Fourteen months before readmission she had been operated upon at another hospital for acute pain in the right lower quadrant of the abdomen; at operation the appendix was not inflamed and the postoperative diagnosis was "acute mesenteric adenitis." Two days after operation jaundice appeared, and then receded to former levels. The patient remained well for a year and then re-entered the hospital because of recurrent jaundice, fatigue and dark urine. The findings at

physical examination were unchanged. The serum bilirubin ranged from 4.1 to 6.0 mg. per cent. Jaundice gradually abated and the patient was discharged.

Stein [20] reported a case from Israel. A twenty year old white man of Persian-Jewish origin came to the hospital in June 1952 complaining of mild jaundice of four years' duration. Jaundice was first noted after a severe respiratory infection; it persisted in a mild form but was intensified by such diversified episodes as infections, unusual physical strain and a surgical operation. He had also noted dark urine and abdominal pain. There was no history of jaundice in the family. On admission, the patient was jaundiced and the liver was tender and slightly enlarged. The serum bilirubin ranged from 3.5 to 6.0 mg. per cent. The urine contained bile but not increased urobilinogen. Other liver function tests and tests for hemolysis gave normal values. A needle biopsy specimen of liver was obtained. The fresh liver tissue was almost black; histologically the liver was normal save for the pigmentation. After discharge from the hospital the patient was able to continue his work as a hospital orderly, although mild jaundice persisted. He was readmitted in October 1954 because of abdominal pain, nausea, vomiting, dark urine and increased jaundice. A tender liver was felt 3 cm. beneath the costal margin. The urine contained bile and increased urobilinogen. The serum bilirubin ranged from 2.0/5.0 to 3.0/8.5 mg. per cent. The following tests gave normal values: serum alkaline phosphatase, serum iron, serum proteins, bromsulphalein retention, cephalin flocculation, thymol turbidity and fecal urobilinogen. The gallbladder visualized very poorly on cholecystography. Histochemical tests on the liver biopsy specimen obtained on first admission gave reactions identical with those we originally described. The patient's symptoms subsided, although jaundice persisted, and he returned to work.

John and Knudtson reported the disease in a brother and sister [12]. The man's case report has already been described as Case 19 in our own AFIP series. The sister (now a woman of thirty-five) first noted jaundice at the age of twelve, and since then has suffered from jaundice, weakness and pain in the right side of the abdomen when jaundice was at its peak. At age twenty she was delivered of her first normal child, but her next two pregnancies ended in spontaneous abortion. Jaundice was aggravated by her fourth pregnancy, and was at its worst in the eighth month when she was delivered of a premature infant. The fifth and sixth pregnancies also terminated in spontaneous abortion. In June 1949 the patient again experienced severe jaundice, abdominal pain and fatigue. The serum bilirubin was 6.9/9.1 mg. per cent; cephalin flocculation test, 2 plus; urine urobilinogen, negative; and prothrombin time, 100 per cent. A presumptive diagnosis of "infectious hepatitis" was made. One month later she became pregnant again. The gallbladder failed to visualize

on cholecystography but there was no evidence of calculi. Near the end of the pregnancy she was hospitalized for induction of labor. The serum bilirubin was 5.6/6.9 mg. per cent; cephalin flocculation test, 3 plus; thymol turbidity test, 13.2 units; serum alkaline phosphatase, 2.2; and erythrocyte fragility, normal. Labor was induced and the patient was delivered of a composite monster. At that time it was thought that the abnormal development of the fetus was caused by infection with "viral hepatitis" in early pregnancy [27]. One month postpartum an exploratory laparotomy was performed. The liver was dark-green to black in color; the gallbladder was filled with pigment-cholesterol stones. Cholecystectomy was performed and a specimen of the liver was taken. The sections of liver were reviewed several years later by Dr. Knudtson and proved identical with those of the biopsy specimen of liver taken from the brother. During the five years after operation the patient felt well but the icteric index remained elevated, ranging between 24 and 28. Two other sisters, both in the late twenties, are reported to have had attacks of "gallbladder trouble" recently, but have not yet been studied.

Brown and Shnitka [22] described a case in a twenty-three year old white man who had been well until April 1950 when he experienced weakness, general malaise, nausea, diarrhea and dark urine; vomiting and anorexia followed. He was admitted to the hospital a month later. There was no family history of jaundice. The patient had not been exposed to hepatotoxins except that he drank a bottle of whiskey each night. On physical examination the significant findings were mild jaundice and tenderness in the right upper region of the abdomen. The urine contained bile and urobilinogen. During the two-week hospitalization the serum bilirubin ranged from 2.2/4.8 to 4.3/8.5 mg. per cent. He was seen again on October 3, 1951, complaining of exacerbation of the previous symptoms; the liver was tender and enlarged. "Chronic hepatitis" was considered. The patient again entered the hospital on January 28, 1953, with weakness, abdominal pain and jaundice. The urine contained bile and urobilinogen. The serum bilirubin was 2.6/4.6 mg. per cent. Other liver function tests gave normal results. The gallbladder was not seen on cholecystography. After a month in the hospital the serum bilirubin fell to 1.9/2.8 mg. per cent. A diagnosis of "cirrhosis of the liver" was made. In December 1954 his symptoms recurred, apparently aggravated by heavy drinking. He re-entered the hospital on January 6, 1955. The serum bilirubin was 3.0/4.8 mg. per cent. Excretion of urinary urobilinogen was increased (ranging from 2.3 to 8.7 mg. in twenty-four hours). The following tests gave normal results: complete blood count, reticulocyte count, erythrocyte fragility, Coombs' test, porphobilinogen, Kahn test, serum proteins, serum alkaline phosphatase, prothrombin time, heterophil agglutinins, thymol

turbidity, cephalin flocculation and bromsulphalein retention. The gallbladder visualized faintly after a double dose of oral dye (telepaque). An exploratory laparotomy was performed on January 14, 1955; the liver was enlarged and dark. The biliary tree and spleen were normal. A liver biopsy specimen showed the characteristic centrolobular pigmentation of parenchymal cells. The patient was discharged two weeks later, clinically well.

Farber and Craig [23] reported the case of a white boy who was admitted to the hospital at the age of five years with a history of intermittent jaundice and pale stools since the age of three months; jaundice began shortly after a series of immunizations. The child's mother, age thirty-nine, had had anemia and mild jaundice all her life. The boy had one sister, who was normal. A maternal grandfather had gallbladder trouble and was jaundiced during the last few years of his life.

The boy had been hospitalized when nine months old, at which time he had jaundice, itching of the skin, dark urine and abdominal pain. The liver was enlarged 4 fingerbreadths but the spleen was not palpable. The peripheral blood was normal. The serum bilirubin was 3.2/5.3 mg. per cent, and the urine contained bile. A laparotomy was performed but no biliary obstruction was found; jaundice continued. When studied again at age five he had jaundice, an enlarged liver, and a spleen that was questionably palpable. There was a mild anemia (hemoglobin 13 gm.); reticulocyte count, erythrocyte fragility and bone marrow studies gave normal results. The serum bilirubin was 3.3/5.4 mg. per cent; the urine contained bile and increased urobilinogen. The thymol turbidity and cephalin flocculation tests and the prothrombin time were normal. A splenectomy was performed. At operation no biliary obstruction was found and a cholangiogram was normal. A biopsy specimen of the liver showed heavy pigmentation of parenchymal cells; histochemical properties of the pigment were identical with those described in chronic idiopathic jaundice. Other histologic changes consisted of mild postnecrotic scarring and a minimal degree of intrahepatic bile stasis. The spleen was slightly increased in weight; follicles were prominent and there was a small amount of hemosiderin in reticular cells lining the sinusoids; there was no pigment similar to that in the liver.

Tamaki and Carfagno [24] reported the case of a thirty-one year old white woman who was admitted to the hospital on January 8, 1956, complaining of vague upper abdominal pain, weakness, dark urine and mild jaundice. She had had recurrent attacks of jaundice since the age of four. In 1946 studies in other hospitals showed a non-visualizing gallbladder (three oral tests); serum bilirubin 1.9/3.1 mg. per cent; cephalin flocculation test, 4 plus. The following were normal: urinalysis, erythrocyte fragility, serum cholesterol and proteins, prothrombin time, brom-

sulphalein retention and biliary drainage. There was no family history of jaundice in her parents or four siblings. The patient had two healthy children, aged three and four years, respectively; pregnancy had not aggravated her jaundice. On physical examination the only abnormalities noted were mild jaundice and slight tenderness in the right upper quadrant of the abdomen. The total serum bilirubin was 3.9 mg. per cent; the cephalin flocculation test varied from 0 to 3 plus; the urine contained bile but no increased amount of urobilinogen. There was slight anemia. The following were normal: erythrocyte fragility, reticulocyte count, Coombs' test, sternal bone marrow, thymol turbidity test, serum alkaline phosphatase, prothrombin time, serum proteins and blood glucose. Intravenous injection of cholografin showed concentration of dye in the gallbladder, without suggestion of gallstones. The diagnosis of "chronic hepatitis" was considered but an exploratory laparotomy was decided upon; the gallbladder and bile ducts were normal and no obstruction was found. The liver was moderately enlarged and slate blue in color; the cut surface of the biopsy specimen was black. Histologically the liver was normal except for the characteristic pigmentation of parenchymal cells in central zones. The patient's postoperative course was uneventful. Two months after operation she was still jaundiced, but asymptomatic; the serum bilirubin was 1.9/2.9 mg. per cent, the cephalin flocculation and thymol turbidity tests, and bromsulphalein retention were normal.

A case was reported by Dr. Hamperl [25] of Bonn, Germany. A thirty-seven year old white man presented with a history of recurrent jaundice for many years; the family history was non-contributory. Jaundice first appeared at age nineteen and lasted about a month. Episodes of jaundice, associated with nausea, vomiting, weakness and abdominal pain, occurred at age twenty-two and twenty-four. At age twenty-five jaundice reappeared; a cholecystectomy was performed and stones were found in the gallbladder. His condition improved somewhat but at age twenty-seven he had another attack of intense jaundice and pain under the right costal margin. At ages thirty-four and thirty-five the serum bilirubin was about 1.0 mg. per cent; the erythrocyte osmotic fragility and electrophoretic pattern of the serum proteins were normal. At age thirty-seven the serum bilirubin was 1.24 mg. per cent; the Takata test, 90 mg. per cent; the urine contained bilirubin, urobilin and increased urobilinogen. The patient was sent to a convalescent home for a rest cure but his condition remained unchanged. The following tests were made when he was admitted to the hospital. The serum bilirubin was 3.5 mg. per cent; bromsulphalein retention, 9.6 per cent; erythrocyte morphology, normal; no increased reticulocytes; no increase in erythroblasts in the sternal marrow. On studies of the coagulation mechanism, prothrombin and factor v were slightly decreased, factor

ix/x slightly elevated, and thrombin-inhibitor markedly elevated; after administration of tromexin® there was a slight decrease of prothrombin and a marked decrease of factor vii; these findings were interpreted as evidence of abnormal hepatic function. An exploratory laparotomy was performed. There were some adhesions in the peritoneal cavity. There was no evidence of obstructive jaundice; the extrahepatic bile ducts and the ampulla of Vater were normal. In the hepatoduodenal ligament and the hilus of the liver there were a few enlarged lymph nodes, one of which was taken for histologic study. Biopsy specimens were also taken from the right and left lobes of the liver. Bacteriological studies of blood, bile and stool showed no pathogenic organisms. The fresh liver tissue was dark brownish black on gross inspection. Histologically, the hepatic architecture was normal except for a slight increase of connective tissue in the portal fields and around the central veins. The main finding was a heavy pigmentation of liver cells in centrilobular zones. After silver impregnation with the Masson-Hamperl technic, some pigment granules, hitherto unnoticed, were demonstrated in Kupffer cells also. The lymph node showed only non-specific hyperplasia. The diagnosis of chronic idiopathic jaundice was made. Hamperl found the pigment not to possess any intrinsic fluorescence, to be non-acidfast, and to give a negative reaction with the periodic acid-Schiff test. He believes the pigment belongs to the general family of lipofuscins but points out that it differs from the usual lipofuscins in size, shape and color of particle size, in fluorescence, and in acidfastness; he considers it a kind of "super-lipofuscin."

Wittekind and Messmer [26] of Heidelberg, Germany reported the case of a thirty-five year old white man who came to the hospital in January 1953 complaining of fatigue, aversion for fatty foods, pain in the upper part of the abdomen, and constant mild jaundice. These symptoms had appeared in 1942 following a severe attack of typhus fever, and had persisted ever since, leading to a diagnosis of "chronic hepatitis." The findings in 1953 were as follows: mild jaundice; liver palpable at costal margin; the urine contained bile and increased urobilinogen; total serum bilirubin 1.46 mg. per cent; non-visualization of gallbladder on repeated cholecystography. The patient's condition remained the same during the next two years. He was studied again in February 1955. His symptoms were unchanged. Laboratory studies gave the following results: blood picture, normal; serum bilirubin, 1.5 mg. per cent, with a positive direct reaction; serum iron 92 gamma per cent; alkaline phosphatase, 4.75 Bodansky units; prothrombin time and serum cholesterol, normal; and bromsulphalein retention, 24 per cent. Bile obtained by duodenal catheterization had a striking green color. At laparotomy the liver and gallbladder were normal but dark green in color. There was no evidence of obstructive jaundice. A biopsy specimen of the liver showed no

abnormalities except for the presence of a particulate brown pigment in parenchymal cells. Histochemical properties of the pigment were similar to those described by Dubin and Johnson [2]. The granules stained dark blue with the Pappenheim stain; they also demonstrated fluorescence with ultraviolet light.

Because of the unusually dark color of the bile, the bile pigments of the gallbladder and urine were studied by means of paper chromatography. The chromatogram of the gallbladder bile showed a strong reaction in the mesobiliviolin zone; only traces of mesobiliviolin were demonstrated in the urine.

In the following nine months the patient was studied many times and liver biopsy was repeated once, but there was no change in his condition.

Klatsky and Huck [27] described the case of a twenty-two year old white soldier who was admitted to the U. S. Army Hospital, Fort Campbell, Kentucky in November 1955 because of jaundice, fatigue, and nausea and vomiting for four days. The family history revealed that the patient's father, aged forty-seven, and one sister, aged twenty-three, had suffered from chronic jaundice; another sister, aged eighteen, was normal. The patient himself had had intermittent jaundice since the age of twelve. At the age of eighteen he had had an acute attack of malaise, nausea and vomiting, and an increase in jaundice. A diagnosis of "hepatitis" was made. His condition had improved gradually over a period of four months. The following year he was operated upon for acute appendicitis; the surgeon noted the tissues were yellow. Postoperatively, deep jaundice developed, followed by a convalescence of three months. For the next two years, the patient tried his hand at several jobs, but had to give these up because of fatigue. He was drafted into the Army in June 1955. He felt fairly well during basic training, but shortly thereafter he became weak and noted nausea, vomiting, increased icterus and a pulsating sensation in the right upper quadrant of the abdomen. On admission to the hospital there was scleral icterus but no other abnormality on physical examination. The blood count and reticulocyte count were normal; Coombs' test was negative. Serum bilirubin was 2.8/4.0 mg. per cent. Bromsulphalein retention ranged from 8 to 15 per cent. Cephalin flocculation test was 2 plus. Thymol turbidity, prothrombin time, serum alkaline phosphatase, serum cholesterol and serum proteins were all normal. The urine contained bile and increased urobilinogen. Cholecystography failed to demonstrate the gallbladder on two trials.

The initial diagnosis was chronic hepatitis and the patient was kept in the hospital for several months, during which time he was fairly comfortable. Because an attempt at needle biopsy of the liver was unsuccessful, a laparotomy was performed on May 3, 1956. The liver was of normal size, but bluer than usual. Other organs were normal. The liver specimen was histologically normal except for a brown pigment in

the parenchymal cells of the centrolobular zones; pigment was also present in the Kupffer cells. The diagnosis of Dubin-Johnson syndrome was confirmed by the Armed Forces Institute of Pathology. The patient was discharged from the military service as unfit for duty.

Karpisek and colleagues [28] recently described a case from Czechoslovakia. The patient was a forty year old white man, who gave a family history of digestive disorders in both parents and chronic jaundice in his grandfather. He was severely jaundiced at birth and continued to suffer from intermittent jaundice thereafter. Jaundice was always aggravated by other ailments and stresses, such as pneumonia at age six, tonsillectomy at age twenty-three, physical exertion, and poor diet. The patient had noted pain in the right subcostal region, weakness, diarrhea and dark urine. In 1942 there was increased urobilinogen in the urine and the serum bilirubin ranged between 2 and 4 mg. per cent; erythrocyte osmotic fragility, galactose test, and duodenal drainage were normal. In 1953 he was hospitalized for fever, arthralgia, jaundice and pain in the right subcostal region. The liver and spleen were not enlarged. The blood counts and liver function tests gave normal values. The gallbladder was displayed very faintly on cholecystography. Beginning in April 1956, following excessive exertion, the patient had three attacks of "biliary colic," accompanied by increased jaundice and bile in the urine. On admission to the hospital, the patient had jaundice and a slightly enlarged, tender liver. The direct serum bilirubin was 7.5 mg. per cent. The following tests all gave normal values: complete blood count, erythrocyte fragility, electrophoresis of serum proteins, and liver function. Intravenous cholecystography with biligraphin showed very little excretion of the dye, but stones were seen in the gallbladder. A cholecystectomy was performed on May 22, 1956; the gallbladder contained several stones, each 1 cm. in diameter, and the bile was unusually dark. There was no evidence of obstruction of the bile ducts; the hepatic ducts and the common bile duct were probed without hindrance. The liver was firmer than usual and had a striking blackish green appearance; it was otherwise normal. The biopsy specimen of the liver was structurally normal but showed pigmentation of parenchymal cells in centrolobular zones.

Jaundice increased after the operation, the serum bilirubin rising to 18.4 mg. per cent four days postoperatively. The jaundice gradually waned and bilirubin disappeared from the urine. The patient was discharged on June 7, 1956, with no clinical jaundice but a serum bilirubin of 3 mg. per cent. From that time on he was free of pain, but mild jaundice developed occasionally.

Lewi and Wietschner [29] described two cases from Israel. The first case was that of a fifty-six year old white man, who had been born in Persia. The past

history and family history were negative. The patient was admitted to the hospital on April 24, 1956, complaining of jaundice and pain in the upper part of the abdomen. His skin and sclerae were yellow. The liver was enlarged 2 cm. and was tender; the spleen was not felt. The urine contained bile and slightly increased urobilinogen. The serum bilirubin ranged from 1.7/2.3 to 2.5/3.6 mg. per cent. The following tests gave normal values: complete blood count, reticulocyte count, prothrombin time, erythrocyte fragility, Coombs' test, serum proteins, blood urea, cholesterol, alkaline phosphatase, cephalin flocculation, thymol turbidity, galactose, hippuric acid and excretion of fecal urobilinogen. The gallbladder was not displayed either by oral or intravenous cholecystography. A biopsy specimen of the liver was dark green in the fresh state; histologically the liver was normal but showed a brown pigment in parenchymal cells. Another specimen of liver obtained three weeks later showed an identical appearance. Serum bilirubin values of the patient's three sons were normal.

The second patient was only briefly mentioned in this case report, but Dr. Lewi [30] kindly sent me a clinical summary. This patient was a twenty-three year old white man who had been born in Persia. The family history was negative. The patient had had jaundice of varying intensity for seven years. At age twenty-two, he underwent a cholecystectomy but only "slight cholecystitis" was described. He was admitted to Dr. Lewi's ward on May 12, 1952, and studied till January 1, 1953. No special findings were noted on physical examination except slight jaundice and slight enlargement of the liver. The urine contained bile. Direct reacting serum bilirubin ranged between 3 and 4 mg. per cent. The following laboratory studies gave normal values: complete blood count, reticulocyte count, Coombs' test, erythrocyte fragility, prothrombin time, serum proteins, serum cholesterol, cephalin flocculation test, thymol turbidity test, serum alkaline phosphatase, fecal urobilinogen. A liver biopsy specimen showed pigmentation of parenchymal cells, but the significance of this was not appreciated until the sections were re-examined by the authors after they read the original article by Dubin and Johnson [2]. The patient was hospitalized in another institution late in 1955, at which time a diagnosis was made of chronic idiopathic jaundice.

OTHER CASES, AS YET UNPUBLISHED

Several physicians in various countries have written to say they have seen similar cases.

Drs. D. L. Bornstein and R. B. Sommer [37] saw a typical case at the Barnes Hospital, St. Louis, Missouri. A seventeen year old boy had had abdominal pain, dark urine and a non-visualizing gallbladder for four years; mild jaundice had been present for one year. The serum bilirubin was 2.0/2.8 mg. per cent, the bromsulphalein retention was 24 per cent, and the flocculation tests were normal. On repeat cholecystog-

raphy the gallbladder visualized faintly and seemed filled with radiolucent stones. Despite this the diagnosis of chronic idiopathic jaundice was made pre-operatively. Cholecystectomy was performed. The gallbladder contained 120 small black calculi. The liver had a dark green-black appearance and showed the histological picture characteristic of the disease. A diagnosis of chronic idiopathic jaundice was made by the pathologist, Dr. Lauren V. Ackerman. Dr. Sommer saw the patient again fourteen months after the operation and a repeat liver profile showed no essential change. An older brother had been jaundiced for years and is now under study.

Five cases have been seen by Dr. C. J. Watson and his group in Minneapolis [32]. Three of these cases were reported briefly by Campbell et al. [33]; all three patients were elderly men with a lifelong history of asymptomatic jaundice; their ages were sixty-eight, seventy-two and seventy-six, respectively. The serum bilirubin was elevated in each case; the one-minute values ranged from 5 to 8 and the total from 9 to 15 mg. per cent. Non-visualization of the gallbladder on cholecystography and abnormal retention of bromsulphalein was demonstrated in two patients. At laparotomy the gallbladder and bile ducts were normal and the liver greenish black in all three cases. Biopsy specimens of liver showed the typical pigmentation of parenchymal cells. One patient, aged seventy-six years, died of arteriosclerotic heart disease and pneumonia; autopsy confirmed the surgical findings as to the normalcy of the biliary system and the pigmentation of the liver.

Dr. F. W. Wigglesworth [34] of Montreal, Canada reported seeing a typical case, proved by liver biopsy, in a seventeen year old boy of Italian origin.

Dr. J. S. Campbell [35] of Ottawa, Canada studied another case proved by biopsy. The patient was an airman from the Royal Canadian Air Force, aged twenty, who had had jaundice and biliuria for ten years but was otherwise in good health. The histochemical properties of the pigment were identical with those previously described.

Dr. A. Nys [36] of Louvain, Belgium also observed a typical case, proved by liver biopsy.

Dr. W. T. Bynum [37] of Oklahoma City, Oklahoma studied a thirty year old man who had noted mild scleral icterus intermittently for fifteen years. There was no family history of jaundice. The liver was enlarged and slightly tender. The icteric index was 25, bromsulphalein retention was 25 per cent, and the urine contained bile. Complete blood count and cephalin flocculation test were normal. The gallbladder was not seen after a double dose of dye. The patient was hospitalized on April 21, 1955, for seven weeks. The serum bilirubin ranged between 1.0/1.4 and 1.7/6.6 mg. per cent and the cephalin flocculation test between 1 plus and 3 plus. The serum alkaline phosphatase was 3.6 Bodansky units. Erythrocyte morphology and fragility were normal. Melanuria was

reported several times by the laboratory. An exploratory laparotomy was performed in the latter part of May. The biliary tract and pancreas were normal. The liver was enlarged, smooth and black. A wedge biopsy specimen was taken; the pathologist described a normal liver except for a pigment in parenchymal cells which he believed to be melanin. Shortly after, the true nature of the disease was recognized. The patient was studied further in the Will Rogers Veterans Hospital in September 1955. Clinical and laboratory data were similar to those previously observed. The following additional tests gave normal results: reticulocyte count, serum proteins, serum lipoproteins, red cell survival time with chromium⁵¹, non-protein nitrogen and urinary urobilinogen. Another liver biopsy specimen was obtained and the histologic picture was identical with that of the first specimen. In general, the histochemical properties of the pigment were similar to those previously described; the pathologist, Dr. Hugh Stout, was of the opinion that the pigment was melanin [38].

Drs. G. E. Burch and C. E. Dunlap [39] observed the disease in a thirty-nine year old Negro woman at the Charity Hospital of Louisiana, New Orleans, Louisiana. This case is noteworthy in that it is the only example, to date, in a Negro person.

On admission to the hospital in September 1954 the patient gave a history of intermittent jaundice of twenty-four years' duration. One sister had died with jaundice. The patient also gave a history of four spontaneous abortions, all at four months. The patient's illness began in 1930 (at age fifteen) with jaundice and epigastric pain. In June 1937 the icterus index was 20. On her first hospital admission in April 1949 she complained of jaundice, abdominal pain and fever. Also, a pericardial friction rub, mild congestive failure and pleural effusion were found on physical examination. There was no sickling or increased osmotic fragility of erythrocytes. The total serum bilirubin was 3.3 mg. per cent; thymol turbidity test, 4.6 units; and zinc turbidity test, 1.5. The gallbladder failed to visualize. It was believed at this time that the patient had had a septic abortion with pelvic thrombophlebitis, pulmonary embolism and jaundice resulting from pulmonary infarction. She was readmitted to the hospital on January 14, 1951. She had a severe anemia (hemoglobin 3.8 gm.) presumably caused by uterine bleeding resulting from fibroids. Examination revealed jaundice, fever, tenderness and rigidity in the right upper quadrant of the abdomen, enlargement of the liver and spleen, vaginal bleeding, uterine fibroids, retinal hemorrhages and a "psychosis." The anemia, which was of the hypochromic microcytic variety, responded dramatically to iron. Again there was no sickling or increased fragility of erythrocytes; the bone marrow was hyperplastic. The total serum bilirubin was 6.8 mg. per cent; thymol turbidity test, 4.3 units; zinc turbidity test, 9.1; prothrombin time, 50 per cent; cephalin flocculation test, 1 plus; and serum alkaline

phosphatase, 3.3 Bodansky units. The gallbladder did not visualize. An excised lymph node showed only subacute lymphadenitis. A diagnostic uterine curettage showed normal secretory endometrium. She left the hospital on February 22, 1951. In January 1953 the patient's mental disturbance was designated "mild organic mental syndrome." She was studied in the out-patient clinic a month later because of weakness, exertional dyspnea, headaches, jaundice, pain in the region of the liver, and occasional nausea and vomiting. Physical examination demonstrated uterine fibroids and an aortic systolic murmur. The total serum bilirubin was 1.8 mg. per cent; bromsulphalein retention, 20 per cent; thymol turbidity test, 5.4 units; cephalin flocculation test, negative; serum albumin, 5.1, globulin, 2.9 gm. per cent. She entered the hospital again on September 29, 1954, complaining of jaundice, nausea, vomiting, fever, abdominal pain, diarrhea and light stools of four days' duration. She was still mentally ill. The results of physical examination were: temperature, 103°F.; blood pressure, 115/75 mm. Hg; pulse, 102/minute; jaundice; liver enlarged 2 fingerbreadths; an aortic systolic murmur; severe generalized abdominal tenderness. The urine contained bile, increased urobilinogen, 3 plus albumin, blood cells and casts; the total serum bilirubin was 5.03/7.10 mg. per cent; icterus index, 47.5; thymol turbidity test, 5.4 units; bromsulphalein retention, increased. The following tests gave normal values; blood count, reticulocyte count, serum alkaline phosphatase, serum proteins, serum iron, blood glucose, blood urea nitrogen and glucose tolerance. The gallbladder did not visualize. Proctoscopy and x-ray studies of the upper and lower bowel showed nothing abnormal. A needle biopsy specimen of the liver was obtained on October 16, 1954. The liver presented the characteristic pigmentation of parenchymal cells, but was otherwise normal; histochemical properties of the pigment were also typical. A diagnosis of chronic idiopathic jaundice was made.

A case was studied by Drs. G. C. Walsh and J. C. Colbeck [40] at the Shaughnessy Hospital, Vancouver, Canada. A thirty-one year old white man, a former Army Officer who had been born in England, was admitted to the hospital on March 26, 1946 for an operation on his knee. A routine urinalysis detected bile in the urine and he was transferred to the medical ward for further study. The only abnormalities noted on physical examination were scleral icterus and an enlarged liver, felt 4 fingerbreadths below the costal margin. The icterus index was 33 units; complete blood count was normal. The gallbladder did not visualize on oral cholecystography. An exploratory laparotomy was performed May 18, 1946. The liver was uniformly enlarged and dark green. The gallbladder and bile ducts appeared normal. The common duct was explored and no obstruction was found, although there was difficulty in probing it. A chole-

cystojejunostomy and enteroenterostomy were performed. A specimen of liver was excised; the liver was histologically normal except for pigmentation of parenchymal cells. The pigment was not believed to be bile, hemosiderin or hemofuscin, and was considered to be some kind of lipochrome. The pigment was diffusely scattered through the lobules but was more concentrated in centrolobular zones; some also appeared in Kupffer cells. Postoperatively, pulmonary atelectasis and marked jaundice developed, the icterus index rising to 80 units. The patient soon recovered, however, and was discharged from the hospital on June 18, 1946. On March 17, 1948, he was readmitted to the hospital for further study. He had remained quite well except for occasional episodes of nausea, flatulence and right epigastric pain, particularly after exertion. The results of physical examination were the same as before. The serum bilirubin was 2.1/2.7 mg. per cent. The following tests gave normal results: blood count, reticulocyte count, erythrocyte osmotic fragility, urine urobilinogen, prothrombin time, serum alkaline phosphatase, cephalin flocculation, serum cholesterol, serum proteins and bromsulphalein retention. A needle biopsy specimen of liver was obtained on March 24, 1948. The tissue was chocolate brown. The histologic appearance was similar to that of the biopsy specimen taken two years earlier: the liver was normal except for heavy pigmentation of parenchymal cells, particularly in central zones. Following discharge from the hospital he was seen annually for pensions examinations; his condition remained the same. On March 22, 1956, he was admitted for hemorrhoidectomy. The sclerae were icteric and the liver was enlarged 2 finger-breadths. The serum bilirubin was 3.0/3.6 mg. per cent; thymol turbidity test, 6.8 units; twenty-four-hour urine urobilinogen, 5.9 mg. (slightly elevated). The following were normal: blood count, reticulocyte count, cephalin flocculation, serum alkaline phosphatase, fecal urobilinogen, glucose tolerance, galactose tolerance, and electrophoretic studies of serum proteins. After operation the serum bilirubin rose to 3.4/4.7 mg. per cent but returned to preoperative levels by the third day.

The patient's brother, a physician, probably has the same disease. He has had intermittent jaundice since childhood, without other abnormal physical signs. Recently, abdominal colicky pain developed. The gallbladder did not visualize on cholecystography but there were opacities in the gallbladder region. Laboratory tests gave the following results: serum bilirubin 1.6/3.8 mg. per cent; thymol turbidity test, 7 units; serum alkaline phosphatase, cephalin flocculation test, and serum proteins, normal.

Dr. Sheila Sherlock [47] of London, England diagnosed the disease in a thirteen year old white boy who was admitted to the Hammersmith Hospital on December 31, 1952, because of intermittent jaundice since five months of age. Attacks of jaundice, oc-

asionally accompanied by vomiting, would last one to seven days and would recur every six to eight weeks. In 1950 he had been studied in another hospital because of jaundice and abdominal pain in the right hypochondrium; the diagnosis was "mild infective hepatitis and mesenteric adenitis." In January 1952 he was admitted to another hospital for recurrent jaundice and abdominal pain. The total serum bilirubin was 1.95 mg. per cent and the alkaline phosphatase was 29 King-Armstrong units (elevated). The following tests gave normal values: blood urea nitrogen, serum proteins, thymol turbidity and erythrocyte fragility. The gallbladder did not visualize on cholecystography. At laparotomy the liver was large and the cystic duct was narrow. A cholecystectomy was performed but bouts of jaundice continued.

On admission to the Hammersmith Hospital the boy had slight scleral icterus but showed no other abnormalities on physical examination. The serum bilirubin was 1.3 mg. per cent; and serum alkaline phosphatase was 32 King-Armstrong units. The following tests gave normal results: complete blood count, erythrocyte fragility, urine urobilinogen, serum proteins, thymol turbidity and zinc sulphate. A needle biopsy specimen of liver was obtained. The liver cells were heavily pigmented with "lipofuscin" in the centrolobular zones; also, there was moderate fatty infiltration. He was readmitted to the hospital on July 11, 1953, for studies on hemolytic anemia. His condition had remained unchanged. Hematologic studies excluded hemolysis; hemoglobin, reticulocyte count, erythrocyte osmotic fragility, autohemolysis, excretion of urinary and fecal urobilinogen, all gave normal results. The serum bilirubin was 1.9 mg. per cent. The following additional tests were normal: prothrombin time, serum cholesterol, serum alkaline phosphatase, thymol turbidity, blood urea nitrogen. He was again admitted to the hospital on June 16, 1955 (age fifteen). Attacks of jaundice had continued, associated with lethargy. In February he had been admitted to an Army Hospital with "pneumonia," at which time jaundice was noted. The patient again showed no abnormalities on physical examination, except for scleral icterus. The serum bilirubin was 1.2 mg. per cent. Bromsulphalein retention was 10 per cent. The following tests gave normal results: blood count, reticulocyte count, prothrombin time, serum cholesterol, serum alkaline phosphatase, thymol turbidity, zinc sulphate, and electrophoretic pattern of serum proteins. Intravenous administration of bili-graphin failed to demonstrate the bile ducts. Another needle biopsy specimen of liver again showed large amounts of pigment in liver cells in centrolobular zones in an otherwise normal liver. The biopsy specimen was sent to Dr. Deegon of Liverpool for special studies. The pigment did not take a Sudan IV stain on frozen section, and was negative for hemosiderin; it did not contain hematin nor did it have absorption bands characteristic of a dipyrromethene. It was

considered that the pigment was probably of the lipochrome type. The serum bilirubin at this time was 3.2/3.7 mg. per cent. It was concluded that this was a case of chronic idiopathic jaundice. In January 1955 the boy's mother had had a cholecystectomy for a cholelithiasis but was otherwise well. Later, determinations of serum bilirubin in the parents gave levels of 0.5 and 1.4 mg. per cent for mother and father, respectively.

Drs. G. P. Pilling and J. B. Arey [42] studied a case in a seven year old white boy of Italian parentage at the St. Christopher's Hospital for Children in Philadelphia, Pennsylvania. The patient was well until February 1956 when, at the age of six, he suffered from a severe head cold which was followed by jaundice and dark urine about March 1. His local physician found bile in the urine and made a diagnosis of "viral hepatitis." After limitation of activity for four weeks the boy felt well and returned to school. In May, dark urine and abdominal pain developed; the cephalin flocculation test was negative. He lost some weight at this time but resumed normal activity and the color of the urine returned to normal. In August, abdominal pains recurred but his physician found nothing abnormal on examination and the boy returned to school. He remained well until January 4, 1957, when dark urine, abdominal pain, headaches and excessive belching and flatus appeared; bile was found in the urine on several examinations.

He was admitted to St. Christopher's Hospital on February 5, 1957. There was no family history of jaundice. Except for mild scleral icterus, there were no abnormalities on physical examination. The serum bilirubin was 0.9/2.4 mg. per cent; the urine contained a trace of bile but was negative for porphyrins and increased urobilinogen. The following tests gave normal values: blood count, reticulocyte count, erythrocyte osmotic fragility, prothrombin time, serum cholesterol, serum phosphorus, serum proteins, serum alkaline phosphatase, thymol turbidity, cephalin flocculation, gamma globulin, and serum glutamic oxalacetic transaminase (31.6 units). On oral cholecystography the gallbladder visualized very faintly after the second dose of telepaque; but no visualization was obtained after intravenous cholangiography. An exploratory laparotomy was performed on February 17, 1957. There was no obstruction of the biliary tract; cholangiograms confirmed this. The liver appeared normal except for a slight greenish tinge. Cholecystectomy was performed and a specimen of liver taken for histologic study. Bacteriologic culture of the bile showed no organisms. Two days after operation the jaundice worsened, the serum bilirubin rose to 3.5/5.8 mg. per cent and the cephalin flocculation test became 2 plus. By February 19, however, jaundice had disappeared and the patient was clinically well. Histologically, the liver was normal except for pigmentation of parenchymal cells. Although the pigmentation was more pronounced in

the central zones, all parts of the lobules were affected. There was no pigment in the Kupffer cells. The pigment was identical with that seen in other cases. The stain for hemosiderin gave negative results; the reaction after periodic acid-Schiff stain followed by digestion was only slightly positive. The gallbladder showed no histologic abnormalities.

OBSERVATIONS

Clinical Data

Incidence. In 1956 there were twenty-three cases of this disease in the Registry of Hepatic Pathology which contained about 8,000 cases of hepatic disease studied by biopsy. The incidence among the general population is unknown. The fact that within a few years fifty cases have come to my attention indicates that, while uncommon, the disease is not rare.

Sex. Among forty-seven cases in which the sex was reported, there were thirty-eight cases in males and nine in females. The exact sex ratio in the general population is unknown; cases in the Registry of Hepatic Pathology are predominantly derived from Armed Forces and Veterans installations and therefore are disproportionately weighted in favor of the male sex.

Ethnic and Geographic Distribution. So far, the disease has been reported only once in a Negro person [39]; all the other patients were white. Thirty-four were Americans, two of these native Puerto Ricans; four Canadians, one having been born in Poland and one in England; five Israelis, four of these Persian Jews; 3 Germans; 2 Britons; France, Belgium and Czechoslovakia are each represented by one case.

Family History. Among the thirty-nine cases in which a family history was obtained there were thirteen patients with a familial history of jaundice; two of these were siblings [12].

Age. The age of the patients at the time the disease was first diagnosed ranged from four to seventy-six years. If it is assumed that the first episode of jaundice represented the onset of the disease, the following distribution is obtained for age of onset: up to one year of age, six cases; four to six years, three cases; ten to fourteen years, ten cases; fifteen to nineteen years, ten cases; twenty to twenty-five years, ten cases; age thirty-one, two cases; age forty-two, one case; age fifty-six, one case. In three other cases the disease was "lifelong"; in five others no data were given. (Fig. 1.)

Symptoms. Of forty-four cases in which data were available, ten were asymptomatic. In the

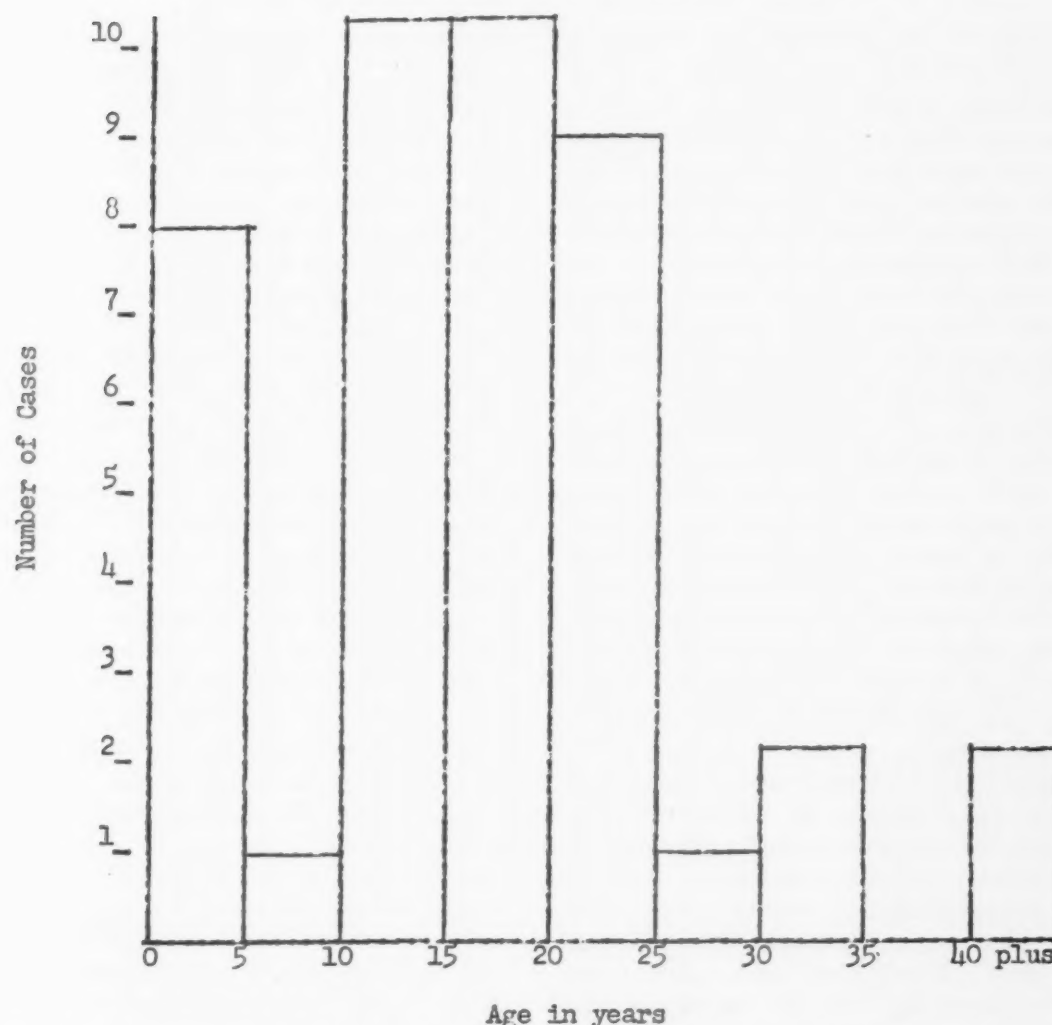


FIG. 1. Distribution of age of onset of chronic idiopathic jaundice, grouped according to five year periods.

other thirty-four all patients complained of abdominal pain, usually in the region of the liver. Weakness or fatiguability was noted by twenty-two patients, anorexia by eleven, nausea or vomiting by fifteen, and diarrhea by six. Heart-

TABLE I
INCIDENCE OF SIGNS AND SYMPTOMS IN CHRONIC
IDIOPATHIC JAUNDICE

Symptoms	Posi- tive (%)	Signs	Posi- tive (%)
Abdominal pain.....	77	Jaundice	100
Weakness.....	50	Enlarged liver	52
Nausea or vomiting....	34	Dark urine	48
Anorexia.....	25	Tender liver	36
Diarrhea.....	13	Pale stools	12
Asymptomatic.....	23		

burn, belching, headaches and nervousness were uncommon symptoms. (Table I.)

Signs. All patients had jaundice, which usually fluctuated in intensity. In forty-two cases with data, the liver was enlarged in twenty-two, and tender in fifteen. Dark urine was noted by twenty of these patients and pale stools by five. (Table I.)

Laboratory Studies

Hematologic Data. Hematologic studies excluded hemolytic jaundice. The erythrocyte count was normal in all but five cases; in four of these there was a mild anemia, while in the other one there was a microcytic anemia (resulting from uterine bleeding) which responded to iron. The erythrocyte morphology was normal. The reticulocyte count (studied in twenty-four cases) and the erythrocyte osmotic fragility (examined in thirty-four cases) were normal.

The Coombs' test was performed in seventeen cases and was negative for antibodies in all of these. Erythrocyte survival time with chromium⁵¹ was normal in three cases so studied. Fecal urobilinogen was excreted in normal amounts by thirteen patients in whom quantities were measured. The prothrombin, bleeding and coagulation times were normal.

Bile and Urobilinogen in Urine. In thirty-five cases in which the urine was examined for bile and urobilinogen, bile was present in twenty-six and increased urobilinogen in twenty-one.

Serum Bilirubin. Serum bilirubin was measured in forty-six cases; both the direct and total bilirubin levels were elevated in all cases in which fractional determinations were made. The levels fluctuated. The maximal levels of total serum bilirubin ranged from 2.4 to 19 mg. per cent; it was over 4 mg. per cent in twenty-seven cases, over 6 mg. per cent in fourteen cases, and over 10 mg. per cent in five cases. The minimal levels fell within normal limits in at least twelve cases.

The direct bilirubin accounted for about 60 per cent of the total bilirubin. In thirty-three cases, using the highest levels in which both direct and total values were recorded, the direct bilirubin ranged from 26 to 86 per cent of the total bilirubin, with a mean value of 60 per cent.

Icterus Index. The icterus index was elevated in seventeen cases in which this test was made. Maximal levels ranged from 13 to 90, most of these values falling between 20 and 30.

Bromsulphalein Test. This test was mentioned in thirty cases. In twenty-three of these bromsulphalein retention was 10 per cent or more at least once. In any one patient the values fluctuated, reaching normal levels at times. Values of over 20 per cent retention were found in ten cases.

Cephalin Flocculation Test. The cephalin flocculation test, performed in thirty-seven cases, gave readings of 3 plus or 4 plus at some time during the illness in thirteen cases, but in no case was the value persistently abnormal.

Thymol Turbidity Test. The thymol turbidity, tested in thirty-one cases, gave values over 4 units in fourteen cases. The levels reached normal values as jaundice subsided.

Serum Alkaline Phosphatase. This test was made in thirty-four cases and was slightly elevated in four.

Serum Proteins and Cholesterol. The levels of serum albumin and globulin were normal. The

electrophoretic pattern of the serum proteins, studied in four cases, was normal. The serum lipoproteins were studied in one case and were normal. The serum cholesterol, measured in most cases, was normal.

Other Laboratory Tests. Excretion of urinary porphyrins was studied in six cases and was abnormally high in one [4]. The following tests were made in some instances and were normal: hippuric acid, zinc turbidity, galactose tolerance, glucose tolerance, serologic test for syphilis, non-protein nitrogen, urea nitrogen, heterophil agglutinins, serum amylase, inorganic phosphorus, transaminase and serum iron.

Cholecystography. Oral cholecystography was performed in thirty-seven cases. The gallbladder was clearly displayed in only one case; in thirty-one cases the gallbladder failed to visualize, and in five cases it visualized only faintly. Intravenous cholografin was used in seven cases in which oral cholecystography was unsuccessful; in four cases (Case 4; Karpisek [28]; Lewi [29]; Pilling and Arey [38]) the gallbladder still failed to visualize; in two cases (Case 7; Tamaki and Carfagno [24]) dye appeared in the gallbladder; in Sherlock's case, with prior cholecystectomy, the bile ducts failed to visualize.

Exploratory Laparotomy

Obstructive jaundice was ruled out by autopsy in one case, by peritoneoscopy in one, and by exploratory laparotomy in thirty cases. In the latter group one case came to autopsy, at which time the normalcy of the biliary tract was confirmed.

Among the thirty cases in which exploratory laparotomy was performed there were five in which the gallbladder contained stones but did not produce biliary obstruction.

Pathologic Data

Source of Liver Specimens. One case was first diagnosed at autopsy. In forty-nine cases biopsy specimens were studied, and in one of these the biopsy findings were later confirmed at autopsy.

Gross Appearance of Liver. The gross appearance of the liver was recorded at laparotomy in twenty-seven cases. In one case the liver was reported to be "normal." In fourteen cases the liver was described as darkly pigmented, but otherwise normal. This was confirmed by autopsy in one of these cases. In nine cases the liver was enlarged and pigmented, but otherwise normal. In one case, studied only at autopsy,

the liver was normal except for the dark pigmentation. In three cases other minor changes were noted that were probably incidental: in Case 1, the liver was first described as "smooth and of normal size" and a year later it was called "atrophic"; in Case 8, the liver was "enlarged, black, and with a tendency towards nodularity"; in Case 22, the liver was small, dark mahogany in color, and had a thickened capsule.

Of twenty-eight cases in which the liver was observed grossly at laparotomy or autopsy a dark pigmentation was reported in twenty-five. Also, there were six cases studied by needle biopsy only, in which the color of the fresh liver tissue was reported as "green-black." In these thirty-four cases the color was variously described as "black" "green-black," "slightly greenish," "slate grey-blue," "purplish blue" and "dark mahogany."

Microscopic Appearance. The most striking finding in all cases was the presence of a coarsely granular brown pigment in parenchymal cells. In almost all cases the pigment had a sharp centrolobular distribution and discolored at least the inner half of each lobule. In three cases (Case 21; Walsh and Colbeck [40]; Pilling and Arey [42]) the pigment was more diffusely scattered in the lobules. The pigment tended to be confined to parenchymal cells except for tiny amounts in Kupffer cells. It was more prominent in Kupffer cells in six cases, but in these there was some incidental focal necrosis of parenchyma which probably resulted in a release of pigment by injured parenchymal cells. Except for pigmentation, the liver was normal histologically. In twelve cases minor abnormalities were found, some of which disappeared in later biopsies. Such changes consisted of mild postnecrotic scarring (three cases), focal necrosis (one case), portal infiltrates (seven cases) and mild fatty metamorphosis (five cases). These changes were probably caused by factors unrelated to the basic disease.

Histochemical Studies. The pigment was neither hemosiderin nor bile [2]. It did not contain hematin nor did it have absorption bands characteristic of a dipyrromethene [47]. The granules emitted a dull brown fluorescence under ultraviolet light [2,26] and were isotropic on polarization microscopy [2]. The granules gave a positive reaction with the performic acid-Schiff method and the periodic acid-Schiff method with digestion [2], although the degree

of positivity varied from case to case. Acid-fastness was negligible or slight [2]. Sudanophilia varied; there was negligible affinity for oil red O stain applied to fixed tissues [2], but John and Knudtson reported strong affinity for this dye in fresh frozen tissue [12]. The pigment did not take Sudan IV stain on frozen section, [22,47] but was darkly stained by Sudan black B in paraffin sections [22]. The pigment was argentophilic [4,22]. It also retained Mallory's basic fuchsin and other basic dyes, such as Giemsa, methylene blue, crystal violet and thionine [22,43]. The pigment reduced Schmorl's ferric ferricyanide but this reaction was abolished by prior oxidation with potassium permanganate [22]. The granules were gradually bleached by 30 per cent hydrogen peroxide [2]. There is apparently a protein matrix in the pigment [22]. The pigment was insoluble in a wide variety of polar and non-polar solvents, including water, various alcohols, ether, acetone, xylene, benzene, chloroform, dilute acids and alkalis [2,4,22].

Other Tissues. Tissues other than the liver were examined in eighteen cases. In two cases autopsy disclosed no pigmentation of tissues except in the liver. In seventeen cases tissues were removed surgically. Pigment similar to that in the liver was found in the bone marrow in one case (Case 13) and in a lymph node near the gallbladder in another (Case 18). In both these cases the pigment was probably released by liver cells and reached new sites via lymphatic or blood stream. The following tissues were free of pigment in surgically removed specimens: lymph node, six cases; skin, three; gallbladder, seven; spleen, two; and one specimen each of muscle, fat, gastric mucosa, endometrium and rectal mucosa. Also, the bone marrow was free of pigment in an undetermined number of cases.

Course of the Disease

Duration. The duration of the disease (according to the last available information) varied from one to more than fifty years. Some patients were still jaundiced at the time we received the latest report on their condition. The duration was zero to five years in fifteen cases, six to ten years in twelve cases, eleven to twenty years in eight cases, twenty-one to thirty years in six cases, and more than thirty years in five cases (including three cases in men about seventy years of age whose disease was "lifelong").

Type of Clinical Course. The onset of jaundice was of three types: (1) insidious, twenty-four

cases, (2) acute, simulating some form of hepatitis, nine cases, and (3) occurring in the wake of some other disease or major stress, ten cases. In seven cases there was no information. In the ten cases in which jaundice first appeared after some major stress, it was precipitated by the following factors: pregnancy, two cases; respiratory infection, one; scarlet fever, one; infectious mononucleosis, one; herniorrhaphy, one; battle stress, one; immunizations, one; typhus fever, one; and anxiety reaction, one. In five of these ten cases, and in at least sixteen other cases, jaundice, once initiated, was aggravated by such factors as intercurrent infections, pregnancy, surgical operations, severe physical strain, alcoholism or mental illness.

The effect of pregnancy on the disease deserves special mention. In the nine cases in women pregnancy was mentioned in seven, and in six of these pregnancy first precipitated or later aggravated the disease. In these seven cases the offspring was normal in four cases and abnormal in three; in one case the child died in the neonatal period of unknown causes; in another case, seven pregnancies resulted in two normal children, four spontaneous abortions, and one monster; and in the third case there were four spontaneous abortions.

In five cases gallstones developed during the course of the disease but evidently did not produce obstructive jaundice. The patients were a thirty-five year old woman, a forty-four year old man, a forty year old man, a twenty-five year old man and a seventeen year old boy, respectively. In two other cases, members of the family had gallstones.

In all cases the jaundice was either intermittent or continuous, and fluctuated in intensity. Many patients had remissions during which the serum bilirubin level was normal. The disease was apparently unaffected by various forms of treatment.

Prognosis. The prognosis is excellent, as judged by the long duration of the disease in many patients, and the absence of progressive hepatic damage in longstanding cases. There is evidently no change in the histologic pattern of the liver with time. One way of measuring this is to correlate the histologic appearance of the liver with the time interval between the onset of jaundice and the first biopsy. In forty-six cases in which this time interval is recorded it was one year or less in ten cases, one to five years in nine cases, six to ten years in eleven cases,

eleven to twenty years in five cases, twenty-one to thirty years in six, and over thirty years in five. Yet in all these the histologic pattern of the liver was normal or showed only minor changes.

Other evidence is derived from studying the time interval between the first biopsy and last in cases in which more than one biopsy was performed. There were fourteen such cases; the time interval was less than six months in six cases, six to twelve months in four, almost three years in three, and four years in one. In none of these was there any significant change in the histologic picture of the liver with time. There was clearly no evidence of progressive hepatic damage. Also, the absence of hepatic lesions other than parenchymal pigmentation in two cases studied at autopsy (one in a four year old boy, and the other in an elderly man with lifelong jaundice) indicates that this disease does not lead to progressive hepatic damage either structurally or functionally. In any given case the amount of pigment in the liver apparently remained the same, even during clinical remissions of jaundice.

COMMENTS

Chronic idiopathic jaundice is an uncommon disease which tends to run in families and to be more common in the male sex. So far only one case has been found in a Negro person, but it is not yet clear whether this is due to a lower incidence or to the greater difficulty in detecting scleral icterus in such persons. The disease has been found in different ethnic groups of Caucasian background in various countries in America, Europe and Asia. In about half the cases the disease begins at birth or at puberty; by age twenty, two-thirds of the patients had already noted jaundice.

Most patients complain of abdominal pain in the region of the liver; weakness, anorexia, nausea or vomiting, and diarrhea are less common. Symptoms tend to occur during bouts of jaundice and disappear as jaundice wanes. Some patients seem to be free of symptoms at all times. Jaundice is recurrent and fluctuates in intensity. The liver is clinically enlarged and tender in about half the cases. Dark urine occurs in 50 per cent of cases and pale stools in about 12 per cent.

The pigment in the serum behaves like bilirubin, as judged by Ehrlich's diazo reaction with diazotized sulfanilic acid. In this disease,

the direct-reacting bilirubin accounts for about 60 per cent of the total serum bilirubin. Recently it was shown by Schmid [44] and by Billing and Lathe [45] that the direct-reacting bilirubin is a glucuronide of bilirubin. Evidently the liver cell extracts indirect water-insoluble bilirubin from the serum and conjugates it with glucuronic acid to make direct bilirubin (bilirubin glucuronide), which is water-soluble. It seems, then, that in chronic idiopathic jaundice the liver cell is able to conjugate indirect bilirubin with glucuronic acid and convert it to direct bilirubin, but it cannot properly excrete the latter into the bile, so that the direct bilirubin is somehow regurgitated back into the blood, either directly or through the lymph. As direct bilirubin accumulates in the blood, it can probably be slowly converted to indirect bilirubin again [46]. Because the bile pigment in the serum is in the direct-reacting, water-soluble form, it can be excreted by the kidney, this explains the presence of bile in the urine in our cases. In Gilbert's disease, on the other hand, all the pigment in the serum is in the form of the indirect (non-conjugated) form; it may be that the defect here is in conjugation, so that the liver cannot adequately link the indirect bilirubin with glucuronic acid. Because there is no direct (water-soluble) bilirubin in the serum in Gilbert's disease, no bile appears in the urine.

The increased amount of urobilinogen in the urine of patients with chronic idiopathic jaundice again suggests an excretory inadequacy on the part of the liver. The dark urine is accounted for by increased amounts of bile and oxidation products of urobilinogen. Bynum [37] states that his patient also excreted melanin in the urine; this finding should be confirmed in other cases.

Additional evidence for inadequate hepatic excretion is found in the retention of bromsulphalein by these patients. Retention of abnormal amounts of bromsulphalein occurs during episodes of jaundice and disappears as jaundice abates.

In about half the cases the cephalin flocculation and thymol turbidity tests give abnormal values while jaundice is present, but return to normal as jaundice subsides. The significance of this is not clear. Serum albumin and globulins are present in normal amounts and the electrophoretic pattern appears normal.

Sprinz and Nelson [4] found an increased

amount of urinary porphyrin in one case, but the meaning of this is not clear.

Other standard liver function tests gave normal results.

A striking finding is the failure of the gallbladder to visualize on oral cholecystography, even though the gallbladder is normal. This occurs even when jaundice is absent. Intravenous cholecystography, used in seven cases in which orally administered dye had previously failed to display the gallbladder, was successful in two cases and failed in the other five. Although one must consider the possibility that the orally administered dye (iopanoic acid) is not absorbed by the intestinal tract, the most likely explanation is that the liver cannot excrete the dye at the normal rate. The greater success in displaying the gallbladder with the intravenously administered dye (iodipamide) may be due to a difference in the chemical structure of the two dyes, or to a more concentrated delivery of the dye to the liver by the intravenous injection.

The liver is normal except for the pigmentation. Minimal histologic changes, other than pigmentation, are found in some cases, but these are either transitory or incidental. There is no histologic evidence of progressive hepatic damage.

The pigment in the liver probably belongs to the family of lipofuscins* [2,4,12,22,25]. It shares with the lipofuscins a centrolobular distribution in liver cells, and such histochemical properties as sudanophilia, argentophilia, isotropism on polarization microscopy, brown fluorescence under ultraviolet light, retention of Mallory's basic fuchsin and other basic dyes, and positive reactions with Schiff reagents.

Furthermore, it is known that liver cells store and probably excrete lipofuscins. Bachmann [47] and Hamperl [48] claim that the liver normally participates in lipofuscin metabolism. It is quite likely, therefore, that the massive accumulation of pigment in the liver in chronic idiopathic jaundice results from defective excretion of some kind of lipofuscin. There are certain differences, however, between this pigment and the ordinary lipofuscins [2,25] which may be a reflection of disordered hepatic metabolism or of an alteration of the pigment as it lies stagnant in the liver cells [25].

The pigment does not contain bile, hemo-

* Some of my more waggish colleagues have suggested that the pigment be called "bilidubin."

siderin, hematin, dipyrromethenes or melanin. Although melanin and the lipofuscins have certain staining reactions in common, there are certain basic differences between them [49,50]; these distinctions also exist between melanin and the pigment of chronic idiopathic jaundice. Melanin does *not* give the following reactions, which were positive in the case of our pigment, namely (1) positive reactions with Schiff reagents, (2) retention of Mallory's basic fuchsin, (3) strong reduction of diamine silver preparations, (4) staining with Sudan black B, and with oil red O under certain conditions.

The pigment occurs in liver parenchymal cells. In some cases it also appears in Kupffer cells in small amounts; but this is probably a secondary event which occurs only when the pigment is liberated by damaged liver cells. This phenomenon is common in diseases of the liver. I have frequently seen lipofuscin and hemosiderin in Kupffer cells in necrotizing hepatic diseases of widely divergent nature. When liver cells are damaged they release two pigments which they normally contain, ferritin and lipofuscins, and these are quickly taken up by the phagocytic Kupffer cells which convert the ferritin to stainable hemosiderin and which retain the lipofuscin or perhaps convert it to ceroid [51,52]. I doubt that the presence of the pigment in Kupffer cells represents an alternative method of excretion, as suggested by Brown and Shnitka [22].

In most cases the distribution of the pigment is sharply circumscribed to the central zones of the hepatic lobules. This suggests that there is a differential metabolic activity in different parts of the liver lobule.

In this disease, the amount of pigment in the liver does not fluctuate in any given case. Apparently, the liver becomes saturated with the pigment, which it cannot excrete, and retains it even during remissions when jaundice disappears. This is in contrast to the normal disposition of lipofuscins by the liver, for Bachmann [47] and Hamperl [48] found that the ordinary lipofuscins in the liver fluctuate in amount, as observed by serial biopsies of the liver.

The amount of hepatic pigment is so abundant that it discolors the liver grossly, giving it a green, slate blue or even black hue. The black appearance of the fresh liver tissue obtained by needle biopsy is characteristic enough to suggest the disease [8].

There is no generalized pigmentation of other

tissues. The pigment may appear in the draining lymph nodes or in the bone marrow as the liver cells release the pigment, which then reaches new sites via lymphatic or blood channels; there it is localized by phagocytic cells, much in the same way as pigment appears in the Kupffer cells.

In about half the cases the onset of jaundice is insidious; in the others jaundice is first noted in association with or in the wake of another disease or major stress. Once instituted, the disease is apparently lifelong; the jaundice fluctuates in intensity and may disappear completely, only to recur later.

Jaundice is precipitated by many factors that constitute a strong metabolic stress. If the disease does not become manifest at birth, it tends to appear at puberty or somewhat later. (Fig. 1.) Jaundice is also precipitated or aggravated by pregnancy, surgical operations, severe physical strain, alcoholism and infectious diseases.

During pregnancy the jaundice gradually becomes more intense, reaching its height in the third trimester, and waning or disappearing completely after delivery of the child. Conversely, it is not yet clear whether or not the disease has an adverse effect on the offspring. One woman, whose jaundice was not aggravated by pregnancy, had two healthy children. Of six women who were jaundiced during pregnancy, three gave birth to normal children and three had abnormal offspring that died *in utero* or at birth. It is estimated that approximately 8 to 10 per cent of all pregnancies end in spontaneous abortion [53,54]. The seven women with chronic idiopathic jaundice together had seven normal and ten abnormal products of conception, adding up to a mortality rate much higher than that in the average population. It is too early, however, to decide whether or not this is the direct result of the hepatic disease.

Another finding that cannot yet be evaluated is the presence of gallstones in five patients, an incidence of 10 per cent. The patients were a seventeen year old boy, a twenty-five year old man, a forty year old man, a forty-four year old man and a thirty-five year old woman, respectively. According to Lieber's statistics [55], the incidence in white males under thirty years of age is less than 1 per cent; in white males between forty to fifty, 4.2 per cent; and in white women between thirty to forty years of age, 8.6 per cent. The incidence of gallstones in our series is higher than expected but it is premature

to decide whether or not the disease tends to cause cholelithiasis. It may also prove interesting to study the composition of the gallstones in this disease.

In any case, the presence of gallstones in a patient with chronic idiopathic jaundice would certainly create a most difficult problem in the differential diagnosis of the presenting jaundice. Even the ordinary case of this disease, uncomplicated by obstruction, will present with pain in the right upper quadrant of the abdomen, a high fraction of direct-reacting serum bilirubin, and a non-visualizing gallbladder on oral cholecystography.

There is no known therapy for the disease. Nevertheless, the prognosis is excellent as regards life expectancy and the absence of progressive hepatic disease. Evidently the disease is compatible with long life; in one-fourth of the cases the disease had been present for more than twenty years. The patients are able to lead a relatively normal existence, except when jaundice is at its height, at which time their activities may be somewhat impaired by weakness, anorexia and abdominal pain. Serial clinical and histologic studies indicate that there is no progressive hepatic damage. The patients should be apprised of the benign nature of their illness and encouraged to lead normal lives lest they become the victim of an overlay of symptoms of psychosomatic origin.

Hemolytic jaundice can be clearly excluded in these cases by appropriate hematologic studies. The reticulocyte count, erythrocyte osmotic fragility, Coombs' test, erythrocyte survival time and excretion of fecal urobilinogen all give normal values. In hemolytic jaundice the parenchymal cells may contain hemosiderin, which appears as a finely granular brown pigment in ordinary sections stained routinely with hematoxylin and eosin, but the Prussian blue reaction will clearly establish that the pigment in question is hemosiderin [2].

Clinically the disease may be readily mistaken for obstructive jaundice. The combination of intermittent jaundice and abdominal pain, dark urine, pale stools, a high fraction of direct-reacting bilirubin, relatively normal values given by the so-called "hepatocellular liver function tests," and a non-visualizing gallbladder, all mimic obstructive jaundice [2]. Nevertheless, the physician's suspicion should be aroused by the history of recurrent jaundice dating from early life, a similar history in siblings, and the

youth of the patient. The serum alkaline phosphatase may be helpful in that it should be elevated in obstructive jaundice and is normal or only slightly elevated in chronic idiopathic jaundice. Finally, a needle biopsy specimen of liver will readily exclude obstructive jaundice and will establish the correct diagnosis. But even here a word of caution is necessary; in some cases of chronic idiopathic jaundice the pigment in liver cells was mistaken for bile pigment and an erroneous pathologic diagnosis of "bile stasis" was made [2]. This error, however, will not be made by a pathologist familiar with liver biopsy specimens, for he will know that in obstructive jaundice bile pigment first appears as small plugs in the bile canaliculi, even if in the later phase it also shows up as coarse granules in scattered parenchymal and Kupffer cells [2,56]. An awareness of this disease and the use of needle biopsy should eliminate unnecessary operations. The danger of unnecessary exploratory laparotomy can be measured by the fact that this procedure was performed in thirty-one of the fifty cases in this series.

Because five of the patients had gallstones, it is theoretically possible that obstructive jaundice may be superimposed upon the basic disease. This has not yet been observed. But should it occur, a needle biopsy specimen of liver should show both hepatocellular pigmentation with the lipofuscin and bile plugs in the bile canaliculi.

Clinically, chronic idiopathic jaundice also resembles Gilbert's disease (constitutional hepatic dysfunction; familial nonhemolytic jaundice). In both disorders we observe recurrent jaundice in young persons, a familial tendency, fatigue, dyspeptic symptoms, aggravation by intercurrent diseases, and a lifelong course. There are several noteworthy differences, however, between the two conditions [2]. Dark urine and bilirubinuria, which occur in chronic idiopathic jaundice, are absent in Gilbert's disease. In Gilbert's disease the serum bilirubin is all or almost all in the form of indirect (unconjugated) bilirubin, whereas in chronic idiopathic jaundice the direct (conjugated) bilirubin accounts for about 60 per cent of the total serum bilirubin. On cholecystography the gallbladder visualizes in Gilbert's disease but not in chronic idiopathic jaundice. Bromsulphalein excretion, normal in Gilbert's disease, is impaired in chronic idiopathic jaundice. Finally, the liver is histologically normal in Gilbert's disease but in chronic idiopathic jaundice is grossly and

microscopically discolored by the brown pigment in parenchymal cells.

Viral hepatitis, infectious mononucleosis and cholestatic (cholangiolitic) hepatitis can be recognized histologically on needle biopsy [56,57]. Moreover, the striking pigmentation of liver cells, so characteristic of chronic idiopathic jaundice, is lacking in these as in all other hepatic diseases [2].

In some cases of porphyria there is urinary excretion of porphobilinogen, which gives a positive diazo reaction. But the entire clinical picture of porphyria sets it apart from chronic idiopathic jaundice. Also, the histologic picture of the liver is different; in porphyria the liver cells contain hemosiderin and the liver tissue emits a red fluorescence under ultraviolet microscopy.

On liver biopsy, the finding of a heavy pigmentation of parenchymal cells in centrolobular zones in an otherwise histologically normal liver is pathognomonic of chronic idiopathic jaundice. The pathologist, nevertheless, may be puzzled by some cases, other than chronic idiopathic jaundice, in which there is an unusual amount of the ordinary lipofuscins in hepatic parenchymal cells. Normally, the liver cells in the centrolobular zones contain a small amount of lipofuscin, but this amount may be increased in cachexia, cancer, old age and, occasionally, even in apparently normal young persons [2]. The lipofuscin in such cases, however, takes the form of fine, dusty particles, in contrast to the coarse granules of the pigment in chronic idiopathic jaundice; moreover, the amount of lipofuscin does not begin to approach the heavy pigmentation seen in the latter disease [2]. These differences are best seen in a comparison of unstained sections. In any case, the combination of clinical findings, laboratory tests and liver biopsy should make the distinction clear.

Nature of the Disease. The evidence at hand indicates that the disease is the result of some inborn error of metabolism. The onset at birth or at puberty and the familial tendency strongly favor this view. The hepatic deficiency expresses itself in excretory difficulties: (1) the liver can conjugate indirect bilirubin with glucuronic acid but presumably has difficulty in excreting the conjugated bilirubin, hence the accumulation of direct-reacting bilirubin in the serum and the spilling over of this water-soluble bilirubin in the urine; (2) the increased amount of urobilinogen in the urine may similarly reflect in-

adequate hepatic excretion; (3) non-visualization of the gallbladder on cholecystography is probably due to inability of the liver cells to excrete the dye [58]; (4) retention of bromsulphalein is again evidence of insufficient excretion; (5) the accumulation of pigment (lipofuscin) in liver cells probably is also the result of inadequate hepatic excretion.

These difficulties in excretion are probably the result of some genetic defect in the liver. It might be considered that the presence of the brown pigment in the liver cells interferes with excretory mechanisms. I would doubt this to be the case, however; in hemochromatosis the liver cells are engorged with hemosiderin with little or no interference in excretion of bile or other substances [51].

Probably both Gilbert's disease and chronic idiopathic jaundice represent examples of genetic defects in liver function; in Gilbert's disease there is a deficiency in the conjugation of indirect bilirubin, whereas in chronic idiopathic jaundice conjugation probably occurs in a near-normal manner but the bottleneck lies in the excretion of the conjugated bile.

In both diseases the liver is teetering on the edge of excretory compensation, and the delicate balance is easily upset by metabolic stresses which put an additional load on an already deficient liver. This explains why a wide variety of apparently unrelated diseases or stress states can precipitate an attack of jaundice.

In any case both diseases must represent highly specific and probably sharply limited inborn defects of liver function which should be studied experimentally. Investigations of such patients would probably yield valuable data on conjugation of bilirubin, excretory mechanisms of the liver, and the metabolism of the lipofuscins.

Nomenclature. Already the nomenclature of this disease is becoming a problem in itself. Originally the disease was independently described as "chronic idiopathic jaundice with unidentified pigment in liver cells" by Dubin and Johnson [2], and "persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells" by Sprinz and Nelson [4]. Obviously both names, while highly descriptive, are too long. Dr. Watson, impressed by the constitutional nature of the disease, and wishing to contrast it with Gilbert's disease, has referred to it as "constitutional hepatic dysfunction of the Dubin-Johnson type" [32]. Others, either because they cautiously preferred to call it a

syndrome rather than a distinct disease process, or because they were discouraged by the lengthy names suggested by the original authors, have used various eponyms [19,22,33]. While eponyms occasionally are preferable to a verbose or inaccurate medical term, the modern tendency is to eschew them. Consequently a shorter term seems desirable. "Chronic idiopathic jaundice" has the virtues of being relatively brief, noncommittal as to etiology, and a direct lineal descendant of the name originally proposed [2]. It may be foolhardy, therefore, to proffer yet another name at this point, but the author has been considering the term "mavrohepatic icterus" despite the fact that it is of Greek rather than English origin. * "Mavrohepatic icterus" simply means "black-liver jaundice" and is a terse, noncommittal way of summarizing our present knowledge of the disease.

Acknowledgments: I am deeply grateful to the many physicians who contributed their cases to this study, which would have been impossible otherwise; I appreciate their generosity in submitting cases, gathering additional data when requested, answering innumerable questions, and even allowing me to study their own manuscripts prior to publication. It would require too much space to mention them individually; but their names appear in the list of references. The Armed Forces Institute of Pathology was likewise most generous in its cooperation: Dr. Leo Krainer and Dr. F. B. Johnson, and Mrs. Ruth Moyer (of the Follow-up Section) gave invaluable assistance. Dr. David Seligson and Dr. Henry Tumen graciously reviewed the manuscript and made many helpful suggestions.

ADDENDUM

Since this article was prepared for publication other case reports have appeared in print.

1. Bartholomew and colleagues described a patient whose disease was first diagnosed at age seventy. At that time the patient presented the characteristic appearance on clinical, laboratory and biopsy studies, although his disease was probably present at least fourteen years earlier. (BARTHOLOMEW, L. G., DEARING, W. H. and BAGGENSTOSS, A. H. Jaundice associated with lipochrome pigmentation of the liver; Dubin-Johnson syndrome. *Gastroenterology*, 33: 302, 1957).

* This name was suggested to Dr. Turner Bynum who used it in his paper [33].

2. Warmoes and colleagues studied the disease in two sisters (twenty and twenty-one years old, respectively) who had chronic jaundice since childhood. Biopsy was performed in the case of the younger girl only and the specimen presented the histologic picture characteristic of the disease. (WARMOES, F., DEDEURWAERDER, R. J. and VAN DEN EYNDE, P. Un cas d'ictère de Dubin-Johnson. *Acta gastro-enterol. belg.*, 20: 525, 1957).

3. DeGroote and co-workers presented the case of a twenty-five year old woman who had suffered from chronic jaundice since the age of seven. Clinical, laboratory and biopsy studies established the diagnosis. (DEGROOTE, J., VANDENBROUCKE, J. and BRUSSELMANS, P. Chronische icterus van het type Dubin-Johnson. *Belg. Tsch. Geneesk.*, 12: 1213, 1956).

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Clinico-pathologic Conference

Uveoparotitis, Skin Nodules, Azotemia and Monocytosis

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

PATIENT A. T., a sixty-eight year old Negro housewife, was admitted to the Barnes Hospital for the fourth time on December 5, 1956. She died on January 28, 1957.

When the patient was first seen in the ophthalmology clinic in September 1955, she complained of sudden loss of vision in the right eye three months previously, and pain in the right eye of three weeks' duration. Examination revealed bilateral cataracts, chalazion, scleritis, iritis and secondary glaucoma. The patient was treated with cortisone eyedrops and atropine with fair improvement in vision. She was referred to the medical clinic where further questioning revealed a ten to twelve month history of anorexia, progressive weakness, constipation, mild dyspnea on exertion, two pillow orthopnea, postural edema, intermittent joint pains with heat, swelling and erythema involving both knees and the left ankle, and a weight loss of 85 pounds (from 300 to 215 pounds).

Physical examination revealed the patient to be a chronically ill, obese Negro woman with a blood pressure of 145/82 mm. Hg. Significant physical findings included a 1 cm. subcutaneous mass on the left thigh, normal fundusoscopic examination, clear lung fields, soft apical and basilar systolic murmurs, and an enlarged liver which extended 13 cm. below the costal margin. There was no significant lymph node enlargement, ascites or edema.

Laboratory data revealed a normochromic and normocytic anemia; the hemoglobin value was 10.2 gm./100 ml. The white blood cell count was 6,350 per cu. mm. with 43 per cent polymorphonuclear leukocytes, 53 per cent lymphocytes, 4 per cent monocytes; 1.5 per cent reticulocytes and 225,000 platelets per cu. mm.

A metabisulfite test for sickling was negative. Cephalin cholesterol flocculation was 3 plus; thymol turbidity, 19.3 units; albumin/globulin ratio, 3.4/4.0 gm.; alkaline phosphatase, 2.5 Bodansky units; serum bilirubin less than 0.8 mg. per cent; calcium, 11.0 mg. per cent; phosphorus, 3.4 mg. per cent; and bromsulfalein retention was less than 6 per cent at forty-five minutes. Roentgenograms revealed left ventricular enlargement, osteoarthritis and hilar calcification; a diverticulum of the duodenum and diverticulosis of the colon. Aspirated sternal bone marrow was cellular with normal myeloid-erythroid ratio. There was a slight increase in plasma cells (2.5 per cent) and reticulum cells (3.0 per cent). The fixed tissue sections of the marrow showed 10 to 15 per cent plasma cells and were thought to be compatible with multiple myeloma. The Sia test for macroglobulins was negative and serum electrophoresis showed a moderate diffuse increase in the gamma globulins. Bone marrow cultures for acid-fast organisms and fungi were all negative. Urinalysis was completely normal and the serological test for syphilis was negative. A Kveim test for sarcoid was negative.

In December 1955, a biopsy specimen was obtained of a subcutaneous lymph node in the right epitrochlear region. Histologic examination of the node failed to show significant abnormal changes, and it was thought to represent "reaction to injury." Lymph node cultures were negative for acid-fast bacilli and fungi; guinea pig inoculation was negative. In February 1956, an intermediate strength P.P.D. tuberculin test was moderately positive, and it was noted that 3 subcutaneous nodules, 1 to 2 cm. in size, had developed on the patient's left forearm. A

TABLE I
SUMMARY OF HEMATOLOGIC DATA

Date	Hemo- globin (gm. %)	White Blood Cells (per cu. mm.)	Reticulo- cytes (%)	Platelets (per cu. mm.)	Seg- mented Neutro- phils (%)	Neutro- phils (%)	Myelo- cytes and Meta- myelo- cytes (%)	Lym- pho- cytes (%)	Mono- cytes (%)
11/21/55	11.6	6,350	1.5	225,000	43	53	4
7/30/56	4,200	4.5	650,000	40	5	1	43	10
10/8/56	8.5	5,400	5.6	660,000	22	4	..	70	4
10/31/56	7.4	18,800	67	1	..	24	6
11/5/56	7.3	7,600	5.7	890,000	34	3	4	34	22
11/26/56	6.6	14,600	2.1	272,000	37	14	5	28	17
12/5/56	5.7	10,050	1.0	229/1000 R.B.C.	51	6	7	23	13
12/20/56	8.7	5,150	0.1	338,000	19	6	1	43	38
1/3/57	6.9	16,850	1.0	10	..	3	18	68
1/10/57	9.4	26,800	0.9	10	..	2	13	74
1/16/57	8.2	34,000	0.5	8	..	2	11	79

surgical biopsy specimen was interpreted as "fibrovascular proliferation with evidence of old and recent hemorrhage; no diagnosis made." A skin biopsy was interpreted as normal.

In 1948, the patient had had bilateral pleuritic chest pain associated with bloody, foamy sputum. She had been treated for pneumonia at another hospital and had recovered completely after thirteen days. Her menses had been normal, but her menopause occurred at the age of forty. The patient had never been pregnant. In 1954, all her teeth had been extracted.

The patient's mother died of ovarian cancer at age sixty-five. One brother died of syphilis at age thirty-five and one sister had diabetes.

Her personal and social history was non-contributory.

The patient continued to complain of weakness, anorexia and fatigue. In July 1956, there was a sudden onset of pain, redness, photophobia and loss of vision in the right eye and, after symptoms had persisted for one week, she was admitted to the Barnes Hospital (McMillan Hospital) for the first time on July 30, 1956.

Physical examination revealed no change from the previous description except for the presence of edema of the right eyelid with conjunctivitis and chemosis, and increased tension of the right eye. In addition there were several 1 cm. subcutaneous nodules on the right elbow and upper arm. There were numerous pigmented papules on the arms and upper back measuring approximately 0.5 cm. in diameter.

The liver was ballotted about 4 cm. below the costal margin; the spleen was not palpable. There was no significant enlargement of the lymph nodes.

Laboratory data may be seen in Table I. The hemoglobin was 12 gm. per cent and the white blood cell count was 4,200 per cu. mm. There were 10 per cent monocytes and numerous clumps of bizarre platelets seen on stained film of the peripheral blood.

The patient was diagnosed as having acute secondary glaucoma. She responded to diamox® and pilocarpine therapy. A bone marrow examination showed normal cellular elements. She was discharged improved on August 17, 1956.

In the interval between admissions the patient continued to have anorexia, weakness and eye difficulties. The glaucoma was well controlled but an episode of hyphemia and scleritis of the left eye developed which responded to local hydrocortisone therapy. The liver was no longer palpable. A 1.5 cm. firm, non-tender lymph node was noted high in the left axilla. The subcutaneous nodule on the right elbow had increased to the size of an egg. Eight days prior to her second hospitalization the patient awoke with swelling, tenderness, redness and heat involving the right side of the jaw and neck. There were no associated chills, fever or sore throat. The swelling progressed, completely closing the right eye, producing moderate dysphagia and pain, and she was readmitted to

the Barnes Hospital (Surgical Service) on September 7, 1956.

The patient was acutely ill and uncomfortable. Her weight was 210 pounds, temperature, 38.5°C.; pulse, 84 per minute. There was a hot, tender, non-fluctuant mass, 15 cm. in diameter in the right submaxillary area extending approximately to the midline. The overlying skin and mucous membranes were markedly edematous and there was weakness of the right facial nerve peripherally. The left parotid gland was moderately enlarged but non-tender. The lachrymal glands could not be palpated. A ventral umbilical hernia 4 cm. in size was described but neither the liver nor spleen could be palpated. The other physical findings were not changed.

Laboratory data may be seen in Table 1. The serum amylase was 76 units. Roentgenograms of the right mandible showed soft tissue swelling without any destruction.

The patient was treated with large doses of penicillin, streptomycin and achromycin®; she was given x-ray therapy to the right parotid region. The swelling subsided and she became afebrile. She was discharged improved on September 16, 1956.

During the ensuing weeks the swelling continued to subside, but the patient subjectively remained incapacitated by weakness. In October 1956, her hemoglobin had fallen to 8.5 gm. per cent; large clumps of platelets were observed on the peripheral blood film but the platelet count was normal. Two weeks before her third admission, a biopsy of the indurated lesion in the right side of the neck was performed. A large superficial mass, thought to be an encapsulated lipoma, was found. Pathologic section showed "salivary gland tissue without unusual histological changes." Two days before admission, sudden swelling developed of the right side of her face and neck. By October 31, when she was readmitted to Barnes Hospital (Surgical Service), this had progressed to such a marked extent that the right eye was swollen shut, the mouth could scarcely be opened, and swallowing was difficult. She had severe pain in the face, a single chill and feverishness.

The temperature was 39.3°C.; pulse, 112 per minute; and blood pressure, 140/80 mm. Hg. There was marked edema of the right parotid area extending across the submental region to the left parotid. The right eye was edematous and completely closed. There was marked in-

duration of the swollen area with tenderness and discoloration of the overlying skin. The left parotid was also enlarged and indurated. Two small firm nodes were palpable in the left supraclavicular area. The liver was palpated 3 cm. below the right costal margin; the spleen was not felt. The remainder of the examination was essentially as before.

Laboratory data may be seen in Table 1. The serum calcium was 9.2 mg. per cent and the amylase was 200 units. Roentgenograms of the chest showed an interval increase of the right hilar node enlargement with some left hilar enlargement as well; there was infiltrate extending out from both hilar areas and moderate cardiomegaly. Roentgenograms of the hands showed a cystic lesion in the right third digit. Roentgenograms of the mandibles revealed marked parotid swelling without bony destruction. Serum electrophoresis showed a decrease in serum albumin and a diffuse increase in all serum globulins.

The patient was treated with penicillin, streptomycin and achromycin® and was given radiation (200 r) to the right parotid area. The temperature slowly returned to normal and the swelling abated, although considerable induration remained. Before discharge a right axillary lymph node biopsy was performed and showed "a scattering of plasma cells and slight reticuloendothelial hyperplasia; no diagnosis made.

Following discharge on November 14, 1956, the parotid swelling continued to decrease. The patient complained continually of weakness and a stuffy nose; she was noted to have a low grade fever (101°F.). Her white blood cell count ranged from 5,300 to 14,600 with a few immature granulocytes and about 4 nucleated red blood cells per 100 white blood cells. A Sia test for macroglobulins showed a faint precipitate. About ten days before her last admission a draining ulcer appeared over the right parotid gland and continuously drained a bloody-purulent material. One unit of packed red cells was given because of progressive anemia, and sulfadiazine therapy was initiated. About two days before admission, a tender fluctuant area 2 cm. in diameter appeared over the left parotid gland. The patient was readmitted for surgical drainage on December 5, 1956.

The patient appeared chronically and acutely ill. Her temperature was 37.4°C.; pulse, 86; respirations, 22; blood pressure, 160/104 mm. Hg. The parotid glands were enlarged bilaterally with firm induration and slight edema of

TABLE II
SUMMARY OF BLOOD CHEMICAL FINDINGS AND URINALYSIS

Date	Blood										Urine				
	Blood Urea Nitrogen (mg. %)	Non-protein Nitrogen (mg. %)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	CO ₂ (mEq./L.)	Ca (mg. %)	P (mg. %)	Miscellaneous*	Output (cc./day)	Protein	Specific Gravity	Na (mEq./L.)	K (mEq./day)	Miscellaneous
11/21/55	..	21	A/G 3.4/4.0	1.028
7/30/56	..	16	0-5 Red blood cells
9/7/56	..	9	11.0	3.4	0-5 Red blood cells 0-5 White blood cells
10/31/56	..	20	1+	1.020	Hyaline casts
12/6/56	..	91	7.8	10.4	A/G 2.1/5.8	...	2+	1.014	10-12 Red blood cells 4-6 White blood cells
12/10/56	85	101	138	...	4.8	16.5	ASO 7,500	900	3+	1.015	4+ Red blood cells, 2 red blood cells Casts, 6-8 White blood cells
12/15/56	73	...	137	108	4.5	15.7	7.8	8.4	725	3+	1.015	5.2	13.5	4+ Red blood cells 8-10 White blood cells
12/20/56	71	...	128	108	4.8	15.3	900	2+	1.007	1+ Red blood cells 2-3 White blood cells
12/30/56	58	...	129	107	4.4	17.2	8.0	4.3	A/G 1.9/5.7 ASO) 500	700	3+	1.008	6.0	8.6	10-15 Red blood cells 5-10 White blood cells
1/17/57	73	...	129	109	5.1	16.1	A/G 2.2/6.1	550	3+	1.010	6.0	9.1	15-20 Red blood cells 5-6 White blood cells
1/25/57	77	...	127	102	5.4	13.3	8.6	5.8	500	3+	1.007	6.0	8.3	15 Red blood cells 30-40 White blood cells

* A/G = albumin/globulin.
ASO = antistreptolysin O titer.

the overlying skin. There was a draining ulcer over the right parotid gland and a fluctuant area over the left parotid gland (2 cm. in size). No enlargement of lymph nodes or lachrymal glands was detected. Proptosis was present bilaterally. The right pupil was fixed and neither fundus could be visualized. The mucous membranes were pale and dry. There was moderate cardiomegaly with a soft systolic murmur heard both at the apex and the aortic area. The lungs were clear. The abdomen was obese; neither liver nor spleen could be palpated. The neurological examination was normal.

Laboratory data may be seen in Table II. Urinalysis for the first time showed 2 to 3 plus proteinuria, 6 to 10 white blood cells per high power field, many red blood cells, a few red blood cell casts, a few granular casts, and epithelial cells. The non-protein nitrogen was 91 mg./100 ml.; calcium, 7.8 mg./100 ml.; phosphorus, 10.4 mg./100 ml.; alkaline phosphatase, 2.4 Bodansky units; cholesterol, 146 mg./100 ml.; amylase, 78 units; albumin/globulin ratio, 2.1/5.8 gm.; cephalin cholesterol flocculation test, 2 plus; thymol turbidity, 17.7 units; serum bilirubin less than 0.8 mg. per cent. The antistreptolysin O titer was greater than 500 units, and C-reactive protein was 3 plus. Cultures from the right parotid ulcer grew beta-hemolytic streptococci and white non-hemolytic staphylococci. The venous pressure was 210 mm. of saline, and the circulation time was 12 seconds (decholin®). An electrocardiogram was normal. Roentgenograms of the chest showed the hilar lymph node enlargement and pulmonary infiltrate as before. Skeletal roentgenograms showed hyperostotic changes in the frontal, parietal and temporal bones; there was hypertrophic osteoarthritis of the spine.

The patient's course was one of gradual deterioration. The results of urinalyses and blood urea nitrogen determinations are recorded in Table II. Although her blood pressure remained in the normal range and there was no edema, the patient was thought to have acute glomerulonephritis secondary to the streptococcal infection of the parotid glands. The left parotid abscess was incised and drained of purulent material which grew a white non-hemolytic staphylococcus. She was treated with penicillin, achromycin and chloramphenicol at different times in an attempt to eradicate the infection. Her course was marked by gradual loss of weight, a reduction in the urine volume, per-

sistence of abnormal urine sediment, elevated blood urea nitrogen, and abnormalities in serum electrolytes. The patient was given six blood transfusions in spite of which she remained anemic. The parotid infection gradually cleared and the ulcer showed granulation and healing. On the twenty-ninth hospital day, an acute uveitis and diffuse bulbar conjunctivitis of the right eye developed which slowly cleared with local pilocarpine and cortisone therapy. A mild hemolytic process was suspected as contributing to the anemia although a direct Coombs' test was negative, and the patient would not permit an erythrocyte survival study using chromium-51. Throughout her hospital course, she showed a progressive elevation in her white blood count to a high of 34,500 per cu. mm. with 78 per cent monocytes, and 14 young monocytes just prior to discharge. On the fortieth hospital day, isoniazid therapy was begun as a further therapeutic measure. During the last two weeks of her hospitalization, the patient refused to cooperate with any further procedures and refused to take her medication and to eat. Under these circumstances arrangements were made for her to be cared for at home. Just prior to discharge she was found to have a urinary tract infection due to aerobacter and she was treated with furadantin.® She was discharged on January 27, 1957.

On the day following discharge, the patient was brought to the Emergency Room with a history of having blacked out while sitting on the commode a few hours before. No convulsions or blood loss in the stool were observed. When the patient was examined, her blood pressure was 86/60 mm. Hg; pulse, 90 per minute; and temperature, 36°C. The physical findings were otherwise unchanged from the day before. The patient's symptoms were thought to be due to her moderate anemia, and she was given a transfusion of 250 cc. of packed red blood cells. Following this, she appeared to be jittery and irrational but complained of no pain. About two hours following the transfusion, she suddenly awoke from sleep with a hot flush, a sense of breathlessness, and was found gasping in a cold sweat. Several minutes later she died.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This patient was a sixty-eight year old Negro woman whose illness extended over a period of a little more than two years. Both her hospital record and her clinic

chart are voluminous; I will not attempt to summarize the clinical data except to note that she presented with uveoparotitis, skin nodules, azotemia and monocytosis. Perhaps we should start with a review of the radiologic examinations. Dr. Humphrey?

DR. HARVEY A. HUMPHREY: Roentgenograms were taken over a period from October 1956 to January 1957. Examination of the chest showed moderate hilar and mediastinal node enlargement. The heart was enlarged but the lung fields were normal. Since sarcoidosis was suspected, films of the hands were obtained. A destructive lesion in the middle phalanx of the right middle finger was noted. This probably represented a small fibrous defect or cyst. Demineralization of the bones with some destruction of cancellous type bone was also seen. The latter is compatible with leukemic infiltration and was evident in the left femur. A film of the skull showed incidental thickening of the frontal bones. Some calcification in the internal carotids was seen. Over the period of observation, the hilar and mediastinal nodes did not change but the heart definitely increased in size. Whether this represented pericardial effusion, or leukemic infiltration of the pericardium and heart is not clear.

DR. REINHARD: This patient had biopsies of two subcutaneous nodules, of the skin, of a salivary gland and of a lymph node. The findings were negative and no specific diagnoses were made. In considering today's case, I would first like to decide what syndrome we are dealing with, and then perhaps we can go on to a discussion of the etiology. There are three syndromes, all of which seem to have features in common with our patient, namely; the Sjögren syndrome, the Mikulicz syndrome and the Heerfordt syndrome. The latter is sometimes called uveoparotid fever and is generally considered to be a manifestation of sarcoidosis. Sjögren's syndrome in the complete form consists of decreased or absent lacrimation with keratitis, conjunctivitis, dryness and atrophy of the membranes of the nose, mouth and throat, enlargement of the parotid glands and chronic polyarthritis. Many patients do not have the complete syndrome, however. Dr. Becker, do you think this patient had Sjögren's syndrome?

DR. BERNARD BECKER: No. She did not have a "dry eye," nor was there any evidence of a dry mouth. The picture presented was of a uveitis with secondary glaucoma. This type of

involvement is not described in Sjögren's syndrome.

DR. REINHARD: In 1892, Mikulicz described a case of symmetrical enlargement of the lacrimal and salivary glands. Microscopic examination of the glands disclosed atrophy of the acinar parenchyma and diffuse replacement by lymphoid cells. In the years that followed, many cases of Mikulicz's disease were reported in patients who actually had sarcoidosis, lymphoma, leukemia or tuberculosis. Thus the literature became very confused. Properly, one should speak of Mikulicz's syndrome associated with sarcoid, leukemia or the like, and the term Mikulicz's disease should be applied to disease of the lacrimal and salivary glands of unknown etiology with the pathological findings described by the author. It is interesting that recent studies have provided evidence that Mikulicz's disease and Sjögren's syndrome may be manifestations of the same entity. Be that as it may, this patient had salivary gland enlargement, and involvement of the uveal tract but no lacrimal involvement. How would you classify this syndrome, Dr. Becker?

DR. BECKER: One may designate an entity as Mikulicz's syndrome when there is salivary gland involvement with or without involvement of the lacrimal glands or the uveal tract. This patient could certainly be classified then, under the Mikulicz syndrome. Heerfordt's syndrome, uveoparotid fever, occurs predominantly in young people; in the age group of ten to thirty years; and very rarely beyond that. There is confusion in the literature regarding the syndrome and its etiology. Most people agree that it is a manifestation of sarcoid although some patients have died with miliary tuberculosis. It would be a convenient syndrome in which to place the patient's ocular and salivary gland manifestations, but I would have several reservations about doing so. Although sarcoid should be the number one consideration in our patient, that disease seems unlikely in view of the negative biopsies and the age of the patient. On the other hand, the fact that she was a Negro would be in favor of sarcoid, as would the eye signs of uveitis. The leukemia and lymphoma group rarely produce iritis. The bizarre thing about this patient's iritis, however, was the fact that she had a hyphemia, that is, a hemorrhage into the anterior chamber. In my experience, and in a cursory review of the literature, this is extremely rare in sarcoid. On the other hand,

hemorrhage into the anterior chamber is described in leukemic infiltration of the iris.

DR. REINHARD: Before we discuss sarcoid in any more detail I would like to have Dr. Eisen comment on the specificity and the reliability of the Kveim reaction.

DR. HERMAN EISEN: In the performance of the Kveim test for sarcoidosis, the following procedure is used: Sarcoidal spleen is homogenized in saline and this extract is injected intradermally into the skin of the patient to be tested. The site of injection is examined six weeks later and if a papule is present, it is biopsied. The histologic appearance of a sarcoid granuloma is required for a positive test. Ultimately then, the test is no better than the judgment of the person who examines the biopsy. Another difficulty in the use of this test concerns the preparation of the antigen which is subject to unknown variations. Some sarcoidal spleens turn out to be satisfactory antigens, in the sense that they give reproducibly positive reactions in clinically proved cases of sarcoid. Other preparations are not satisfactory. Moreover, even preparations which are active in the fresh state, deteriorate with time and must be restandardized from time to time. In the hands of Carl Nelson, who has been studying this problem over a number of years, it is a reliable test. In clinically active and proved cases of sarcoid, he finds a high incidence of positive reactors but not 100 per cent. In a recent paper,* fifty-three of fifty-six patients with documented sarcoid in an active phase, gave a positive test. However, three of the fifty-six did not and this means that in the very best hands, with an excellent preparation of antigen, there is still a chance of getting a negative test. Further, out of several hundred patients tested, only one patient with active tuberculosis gave a positive test.

DR. REINHARD: It would appear that there are two quite specific laboratory procedures for the diagnosis of sarcoid. One is the Kveim test and the other is biopsy of the involved tissue. Both procedures were negative in this patient. Despite this, there are many features about the case today which are very suggestive of sarcoid. Dr. Moore, I wonder if you would discuss this problem?

DR. C. V. MOORE: I certainly agree that there are many clinical manifestations here which strongly suggest sarcoid. However, in active

sarcoid it would be extremely unusual to have negative biopsies of skin, subcutaneous nodules and lymph nodes. The skin biopsies, in particular, tend to be, if not definitive, suggestive enough so that the histopathologist strongly suspects the diagnosis.

DR. REINHARD: Is it not also true, however, that almost any other likely primary diagnosis which one would postulate would also be expected to produce positive biopsy findings, particularly with lymph node biopsy?

DR. MOORE: That is absolutely true. I suppose you are referring to the possibility of monocytic leukemia. If this patient had monocytic leukemia, it would be absolutely phenomenal that not one of these many biopsies gave a positive result.

DR. REINHARD: Now, how about the hyperglobulinemia and the monocytosis? Are these findings observed in sarcoid?

DR. MOORE: Hyperglobulinemia is not at all unusual in sarcoid. However, the white blood cell count is usually below 10,000 per cu. mm. and very rarely above that level. One may see a monocytosis of 20 or 25 per cent in patients with sarcoid which would represent a true monocytosis. I have been unable, thus far, to find any instance in which a monocytosis of the degree exhibited by this patient was actually recorded in sarcoid. However, it is certainly not an impossibility.

DR. REINHARD: Dr. Karl, would you like to comment on the diagnosis of sarcoid?

DR. MICHAEL KARL: I can only agree that in spite of the fact that there are many manifestations of sarcoid present, the absence of positive histological biopsies would be strong evidence against it. I cannot agree that the age is strong evidence against the diagnosis since we have seen proved sarcoid in patients in this age group.

DR. REINHARD: Let us now focus our attention on this patient's hyperglobulinemia with particular emphasis on the fact that there was a diffuse increase in gamma globulin. You will recall that there was also an increase in plasma cells in the bone marrow. Dr. Brittingham, what are some of the conditions which may produce this change?

DR. THOMAS BRITTINGHAM: The outstanding conditions producing hyperglobulinemia are multiple myeloma and, if it is a different disease, macroglobulinemia. The next most important condition would be chronic infection of any kind, of which lymphogranuloma venereum and

* NELSON, C. T. and SCHWIMMER, B. Specificity of the Kveim reaction. *J. Invest. Dermat.*, 28: 55, 1957.

leishmaniasis cause the greatest globulin elevations. One must also consider hepatic disease, and here the highest globulin values occur in postnecrotic cirrhosis. Any of the group of connective tissue diseases such as systemic lupus erythematosus may produce a marked hyperglobulinemia. Finally one must consider a miscellaneous group of diseases including the leukemias, lymphomas, carcinomas, reticuloses and sarcoidosis.

DR. REINHARD: I am not aware that hyperglobulinemia is common in chronic monocytic leukemia. Dr. Moore, do you have any information on this?

DR. MOORE: No, I cannot recall having observed it in monocytic leukemia.

DR. REINHARD: Let us summarize the hematologic findings for just one moment. You will note that terminally the patient had a white blood cell count of 34,000 per cu. mm. with 78 per cent monocytes. I understand that most of our hematologists have reviewed this patient's blood and bone marrow slides. Dr. Moore, you were one of them. I wonder if you would comment on the appearance of the monocytes. Were there significant numbers of abnormal or immature monocytes or were these normal mature cells? And further, could you find any Auer bodies?

DR. MOORE: There were significant numbers of abnormal monocytes and quite a few young forms which I would call monoblasts. If these slides had been presented to me without any clinical data, I am sure that I would have made the diagnosis of monocytic leukemia. I examined these slides for several hours and did not find Auer bodies. I understand however, that both Miss Minnich and Dr. Harrington saw several cells with Auer bodies which satisfied them. This type of observation is a little bit like hearing a diastolic murmur. If they actually saw Auer bodies, then I think the diagnosis is certain. If they place a question mark behind those Auer bodies, that is a different story.

DR. REINHARD: Dr. Harrington, I wonder if you would comment on this?

DR. WILLIAM HARRINGTON: I saw only the one cell that Miss Minnich showed me and I believe this was a true Auer body. I looked by myself later on and could find no others.

DR. REINHARD: Dr. Gabriel Izak (Hadassah Medical School, Jerusalem, Israel) is visiting us, and I would like to have him participate in this discussion. Dr. Izak, you also studied these slides. I wonder if you think that this patient

had monocytic leukemia or would you think she might have had a monocytic leukemoid reaction?

DR. GABRIEL IZAK: I certainly would have diagnosed monocytic leukemia on the basis of the morphology of the cells and the percentage of immature and mature monocytes. There are a number of things, however, which place doubts in my mind with regard to this diagnosis. One, is the fact that when there is an acute outpouring of monocytes as we presume this patient had, I would have expected more immature forms than were actually seen. Secondly, if this is a monocytic leukemia, I would have expected a decrease in the total platelet count which did not occur in this patient.

DR. REINHARD: We have Dr. Germann Ducach (University of Chile School of Medicine, Santiago, Chile) with us. Dr. Ducach you also examined the slides in great detail. Would you give us your opinion?

DR. GERMANN DUCACH: From the morphological aspects of the cells we saw, we think that this patient had a form of acute leukemia most probably a form of monocytic leukemia. I saw a few myeloblasts in addition to immature monocytes, and I would consider it perhaps to be the Naegeli type of monocytic leukemia.

DR. REINHARD: There are certainly some things about this case that disturb me although I also would agree that, from looking at the last blood film on this patient, the diagnosis of monocytic leukemia would have to be made. Let us consider some of the more common causes of marked monocytosis or, if you will, a monocytic leukemoid reaction. Dr. Moore, do you think such a reaction is worthy of serious consideration in our case?

DR. MOORE: A true monocytic leukemoid reaction with a high total monocyte count as well as a high percentage of immature monocytes in the peripheral blood has been described in tuberculosis. Wintrobe mentions one such case. I have seen one. Moderately high values may be seen in Hodgkin's disease but the only situation that I would single out here, as being able to cause this degree of leukocytosis and this high percentage of abnormal monocytes would be tuberculosis.

DR. REINHARD: Are you implying that you think this patient might have had tuberculosis?

DR. MOORE: One can make the same comment about the biopsy specimens as was made about sarcoidosis. It would be extraordinary

that a diagnosis of tuberculosis would not have been made over this two year period.

DR. REINHARD: If this patient did have monocytic leukemia at the time of her death, we are faced with the problem of trying to explain the period when she had subcutaneous nodules, swollen salivary glands, lymph node enlargement and hepatomegaly without monocytosis in the peripheral blood and without any changes in the bone marrow suggestive of monocytic leukemia. Dr. Loeb, would you discuss the concept of preleukemia?

DR. VIRGIL LOEB: Preleukemia is a term which has been used by several groups of investigators to describe early atypical findings noted in patients who ultimately died of leukemia or one of the lymphomatous diseases. In a sense it can be considered a retrospective diagnosis which can therefore give us little comfort. It is applied primarily to patients who have various combinations of anemia, leukopenia, neutropenia, and/or thrombocytopenia, with active bone marrows and usually without splenomegaly. The one common denominator is the observation that at some time or other leukemia develops, usually of the acute form, or one of the malignant lymphomas. It really does not add anything to the discussion to say that if this patient is shown to have leukemia at autopsy, she had had preleukemia during the time that she was under observation. Whether preleukemia is actually an entity and is an atypical form of leukemia or whether it simply represents a state which is ultimately converted to leukemia obviously cannot be answered. Numerous bizarre clinical examples of so-called "refractory anemia" or "hypersplenism" have ultimately developed into leukemia and we are limited by our diagnostic ability to categorize the disease in these early stages.

DR. REINHARD: Dr. Loeb, of the cases reported by Block what type of acute leukemia developed most frequently?

DR. LOEB: In the majority of cases reported by Block* and by Meacham† acute myelocytic leukemia developed ultimately. However, Meacham has reported two cases of monocytic leukemia which started out very much like this case with anemia, granulocytopenia, and

* BLOCK, M., JACOBSON, L. O. and BETHARD, W. F. Preleukemic acute human leukemia. *J. A. M. A.*, 152: 1018, 1953.

† MEACHAM, G. C. and WEISBERGER, A. S. Early atypical manifestations of leukemia. *Ann. Int. Med.*, 41: 780, 1954.

bizarre increases in plasma cells and in reticulum cells in the marrow. It should be pointed out that the "preleukemic" phase of patients reported with this syndrome lasted, on the average, almost two years before the diagnosis became definitive.

DR. REINHARD: I am inclined to think that this term does highlight a point of great importance. In certain cases of leukemia, and in my own experience, this has been true primarily of monocytic leukemia; the patient gives a history of symptoms over a period of months or even years during which time examinations of the blood and bone marrow did not enable us to make the diagnosis. So that although the term adds nothing, it is important to remember that this patient ended up with findings that we think perhaps are indicative of monocytic leukemia and yet during the early stage of the disease, the blood and bone marrow findings were not diagnostic.

Dr. Bricker, this patient died of uremia. I wonder if you would discuss the laboratory data and tell us whether you think she had renal failure due to Boeck's sarcoid, leukemic infiltration of the kidneys or some other type of renal disease unrelated to her uveoparotid-hyperglobulinemia-monocytotic syndrome?

DR. NEAL BRICKER: In 1955, this patient had a negative urinalysis. In September 1956, she had a normal non-protein nitrogen. In December 1956, three months later, she was seen to have advanced renal insufficiency, characterized by severe azotemia, microscopic hematuria and proteinuria. Between these periods, and indeed, before September 1956, she was noted to have microscopic hematuria. Subsequent to December when she presented with advanced renal insufficiency, her renal function stabilized and rather than progressive deterioration, there was some suggestion that her filtration rate improved as evidenced by a fall in blood urea nitrogen and in phosphorus. In the last phase she became oliguric. From this information one can conclude that the renal lesions must fulfill the following criteria: (1) they must be diffuse; certainly a scattered lesion would not result in this type of renal insufficiency, and, (2) they must have had a destructive initial impact and thereafter, stabilized. One suspects that this lesion must be located predominantly in the glomerulus as evidenced by the hematuria and especially the red cell casts, by the proteinuria and perhaps by the observation that in the

presence of marked azotemia, the patient elaborated a urine which was relatively free of sodium. The latter suggests that she had a low filtration rate per functioning nephron. Among the probable lesions that should be considered, I think glomerulonephritis must lead the list. In favor of this is the streptococcal infection, the fact that this disease is characterized by a destructive initial impact followed by variable rates of progression, and the fact of course that it is a glomerulitis. Although it is unusual for an acute exacerbation of chronic glomerulonephritis to be followed by persistent renal insufficiency the presence of hematuria on two occasions prior to December 1956 would certainly suggest that she may well have had a lesion before the development of renal insufficiency.

DR. REINHARD: Would these observations be compatible with the concept that she had monocytic leukemia coexisting with an acute exacerbation of chronic glomerulonephritis?

DR. BRICKER: I think the possibility is excellent Dr. Reinhard, because she certainly had a mixed lesion. Let me just briefly mention the other possibilities. Sarcoid may very well produce renal insufficiency and patients may die in uremia. The lesions are either secondary to hypercalcemia which develop in perhaps 20 or 40 per cent of patients with sarcoidosis or there may be diffuse sarcoid infiltration of the kidneys. Finally patients with sarcoidosis have an inordinate degree of pyelonephritis. With regard to leukemia, the lesion would have to be diffuse and infiltrate both kidneys. Other lesions which involve the glomeruli such as amyloidosis, either with or without coexisting multiple myeloma, must also be mentioned.

DR. REINHARD: Which diagnosis do you consider the most likely one?

DR. BRICKER: She probably did have glomerulonephritis. The chances are good that we will also find some pyelonephritis but the pyelonephritis will not be the major lesion and finally, I think she is going to show one of the other infiltrative lesions which we mentioned. I am not at all sure which one.

DR. REINHARD: Our time is up so we are going to have to draw the discussion to a close. In closing I would like to ask everybody who has participated in the discussion to vote on the question of whether this patient had monocytic leukemia or a monocytic leukemoid reaction due to some other cause. Those who believe this patient did have monocytic leukemia, please

signify by raising their hands. Eight in favor of monocytic leukemia. Those who believe this is a monocytic leukemoid reaction due to something else, signify by raising your hand. Three votes. Does anybody wish to make a primary diagnosis of sarcoid, with a glomerulonephritis? Does anybody wish to make a primary diagnosis of tuberculosis? One vote. My final diagnosis is monocytic leukemia. I think this patient had an acute exacerbation of chronic glomerulonephritis together with leukemic infiltration of the kidney, terminally. The exotic possibility that she might have sarcoidosis with a monocytic leukemoid reaction cannot be excluded. Certainly tuberculosis is an outside possibility but I think it very unlikely. Dr. Rosenberg will begin the discussion of the findings at postmortem.

PATHOLOGICAL DISCUSSION

DR. BARBARA ROSENBERG: Significant external findings were limited to evidence of recent weight loss and generalized but moderate enlargement of superficial lymph nodes. The left parotid gland was enlarged to about twice normal size while the right was small and scarred. The pericardial sac was distended by 700 cc. of blood tinged fluid. Both the visceral and parietal pericardium were covered by a thick layer of fibrin. The heart was enlarged (510 gm.) and there was a scar of an old infarct in the anterior portion of the interventricular septum. A small gray thrombus entirely occluded the lumen of the left anterior descending coronary artery. The mitral valve was slightly thickened and along its closing edge were several small nodules. The lungs were slightly hyperemic but otherwise within normal limits. Grossly the liver and spleen were of usual appearance and size. The kidneys were twice normal weight. The surfaces were slightly granular and a few scattered petechiae were present. Several circumscribed white nodules (2 to 3 mm. in diameter) were noted on the renal surfaces as well as numerous smaller punctate yellow foci. The corticomedullary junction was ill defined. Some recent hemorrhage had occurred within the renal pelvis. The mucosa of the urinary bladder was hemorrhagic and contained numerous small white cysts.

The lymph nodes were moderately enlarged and on section many were homogeneous and yellowish gray. The bone marrow was red and moderately soft except in the femur and tibia where it was softer and pale brown.

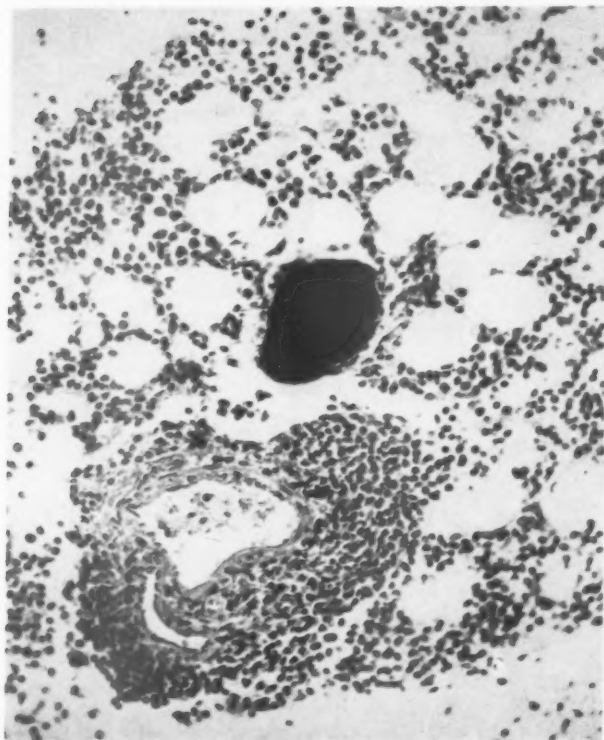


FIG. 1. Hematoxylin and eosin stained section of the femoral bone marrow. There is a distinct perivascular distribution of the cellular infiltrate. Some residual adipose tissue is evident and centrally there is a spicule of bone. Original magnification, $\times 210$.

DR. SARAH LUSE: Microscopically, throughout most of the organs and the bone marrow the tissue was diffusely replaced by leukemic infiltrate. It was comprised of both myelocytic and monocytic cells. Thus, the microscopic findings are consistent with a diagnosis of the Naegeli type of monocytic leukemia, or of acute myelocytic leukemia. In some portions the bone marrow was completely replaced by leukemic cells, while elsewhere, as in Figure 1, from the femur, the infiltrate was spotty and localized about blood vessels. The nuclei varied in form but many were bilobed or reniform. Within the cytoplasm of these cells there were occasional granules, some of which were of the type seen in eosinophilic myelocytes. Focal fibrosis and necrosis were present within some areas of leukemic infiltrate, undoubtedly secondary to the therapy which had been given. Infiltration of the mitral valve by leukemic cells is an interesting and unusual variant of the disease. As was previously mentioned there were 700 cc. of serosanguineous fluid present within the pericardial sac. The pericardial effusion must have been contributed to by at least two lesions.

FEBRUARY, 1958

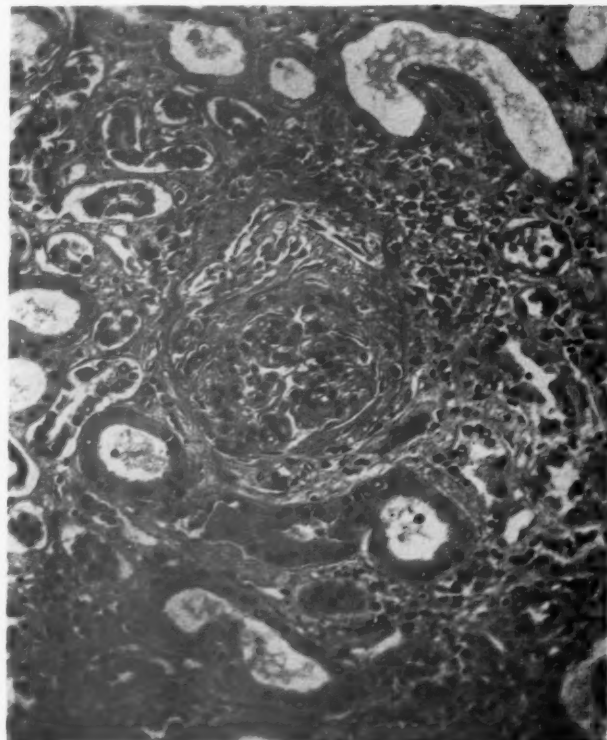


FIG. 2. Hematoxylin and eosin stained section of the kidney. There is distinct thickening of Bowman's capsule. In the upper portion of the glomerulus there is fibrosis and scarring of the glomerular tuft. Some cellular infiltrate is present within the glomerulus and the periglomerular renal tissue. Original magnification, $\times 210$.

Firstly, this woman had a heart scarred by a previous myocardial infarct; a heart which showed distinct evidence of dilatation and which weighed 510 gm. Secondly, there was a recent leukemic infiltrate in the mitral valve extending into the myocardium and pericardium. I think that both myocardial failure and leukemic infiltration contributed to the formation of fluid, and that the pericardial effusion was the immediate cause of death.

Diffuse leukemic infiltrate contributed greatly to the hypertrophy of the kidneys. However, it was by no means the major renal lesion present as can be seen in Figures 2 and 3. The infiltrate had merely been added to a kidney in which there was profuse evidence of glomerulonephritis. In Figure 2 one of the more advanced lesions within the glomeruli is demonstrated. The majority of glomeruli were involved in some manner, although most to a less severe degree as is seen in Figure 3. Frequently a portion of the glomerular tuft was scarred while other parts of it were relatively normal. Precipitated protein and extravasated erythrocytes were present within Bowman's capsule. The mucosa

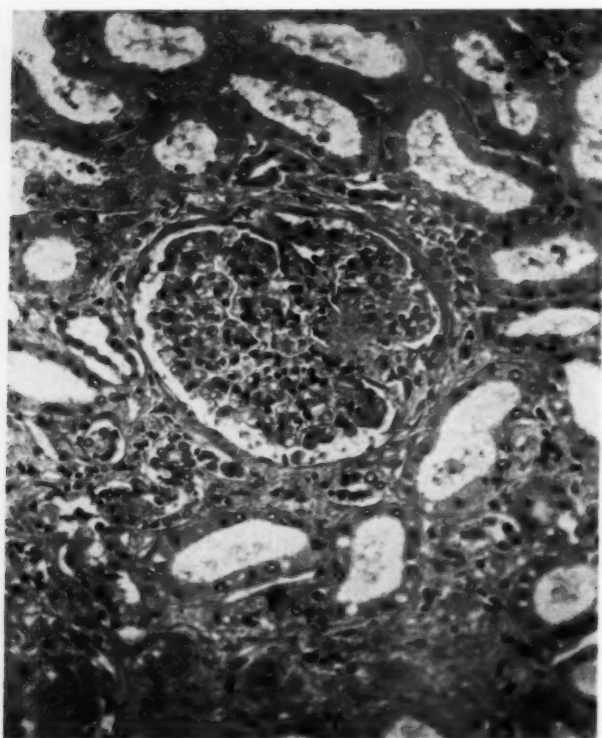


FIG. 3. Another section of the kidney in which the scarring within the glomerulus is less marked than in Figure 2. There is a focal zone of adhesion between the tuft and the capsule which is slightly thickened. Extravasation of erythrocytes is seen in the capsular space. Original magnification, $\times 210$.

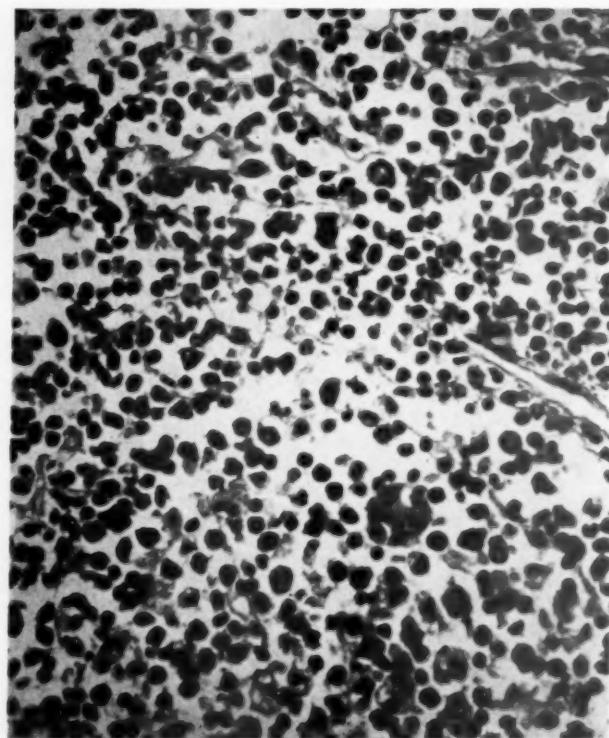


FIG. 4. Section of the lymph node from the periaortic region. In this section there is only scant evidence of the normal lymphoid cell population. Many larger cells are noted as well as the loss of normal architecture. Original magnification, $\times 470$.

of the urinary bladder was of incidental interest as it was almost entirely replaced by lesions of cystitis cystica.

DR. MOORE: Dr. Luse, what did the lymph nodes show?

DR. LUSE: The lymph nodes showed three different patterns. Some were extremely scarred with zones of hyalinization and only a few interspersed lymphoid cells. In other nodes there was evidence of hyperplasia of the reticuloendothelial cells with relatively little leukemic infiltrate, while in still others, particularly in the periaortic region there was definite leukemic infiltration and replacement as can be seen in Figure 4.

Final anatomical diagnoses: Acute myelocytic leukemia (Naegeli type of monocytic leukemia);

leukemic infiltration of the kidneys, liver, spleen, epicardium and endocardium (including mitral valve), urinary bladder, serosa of sigmoid colon, uvea, lacrimal gland, subcutaneous tissue, and lymph nodes; chronic glomerulonephritis; hemorrhagic foci in skin, subcutaneous tissue, gastrointestinal tract and renal pelvis; organized recanalized thrombus in left anterior descending coronary artery; old infarct of myocardium of anterior portion of interventricular septum; acute and chronic passive hyperemia of liver, moderate; lungs, slight; hypertrophy and dilatation of heart (510 gm.); fibrinous pericarditis; serosanguineous pericardial effusion (700 cc.); cystitis cystica, advanced; diverticulum of second portion of duodenum; chronic diverticulitis of sigmoid colon; incarcerated umbilical hernia containing omentum; chronic synovitis, left knee.

Case Reports

Primary Laryngeal Blastomycosis*

Review of the Literature and Presentation of a Case

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BLASTOMYCOSIS was first described in 1894 by Gilchrist [7]. Although over 500 cases have been reported in the literature, only twelve of these have had primary laryngeal involvement [2-9,23]. The diagnosis of primary laryngeal blastomycosis is often difficult to make, and it is so frequently confused with tuberculosis and carcinoma of the larynx that a review of the literature and presentation of a recent case is believed to be justified.

The epidemiology of blastomycosis is poorly understood. The greatest number of cases have been reported from the north central and south-eastern states. In personnel closely associated with patients suffering from blastomycosis the disease does not develop nor do they have a positive blastomycin skin test [25]. Isolated instances of blastomycosis have been reported in animals but no definite animal reservoir has been established [23]. A large percentage of patients with blastomycosis are laborers or agricultural workers. Because of this it has been suggested that the mode of transmission may be related to soil or soil products [17]. Although there have been reports of the isolation of blastomyces or blastomyces-like fungi from the homes of patients with blastomycosis [10], cultures of random soil samples from epidemic areas have consistently failed to reveal the presence of the fungus. However, *Blastomyces dermatitidis* has been grown experimentally in the laboratory in soil which had been autoclaved prior to inoculation [17].

Patients with blastomycosis have ranged in age from nine to seventy-one years, most of them falling into the twenty to forty year age group

[12]. There is approximately a 9 to 1 male to female ratio [12] and a 2 to 1 Caucasian to Negro ratio in the reported cases [11-13]. More than 60 per cent of the symptomatic patients have the disseminated form of the disease [17] and in these patients the systems involved, in diminishing order of frequency, are: pulmonary, cutaneous, osseous, reticuloendothelial, genitourinary and central nervous system [17]. The mortality rate associated with disseminated blastomycosis not treated with stilbamidine has been estimated to be between 78 and 92 per cent [12].

The blastomycin skin test is positive in approximately 56 per cent of patients with active disease [16]. A positive complement fixation test has been noted in about 53 per cent of the patients and is considered suggestive of active disease if the titer is 1:4 or greater [17]. Smith [18] has pointed out that patients with recent pulmonary invasion or localized involvement of the skin tend to have a positive skin test and a negative complement fixation test. He also observed that in patients with extensive involvement the skin test is usually negative while the complement fixation test is either positive or negative. From these observations he suggests that these tests may be used for prognostic purposes; a positive skin test with a negative complement fixation test offering the best prognosis.

The etiologic agent is a 6 to 15 microns [9], budding, double-contoured organism which can be detected by hematoxylin and eosin stains, but is more easily identified with a periodic acid-Schiff stain. Budding is not invariably present. The organisms in the tissues are always in the

* From the Ohio Tuberculosis Hospital, Columbus, Ohio.

yeast phase and mycelia have never been reported in the infected tissues of man or animals. Isolation of the organism may be achieved by culture. Growth occurs in one to two weeks after inoculation but the culture plates should be kept for at least four weeks before reporting no growth. It has been suggested that culture media containing blood may occasionally be necessary for primary isolation of the fungus. Inoculation of animals is not a reliable procedure as the fungus may fail to kill or to produce lesions in the animal. However, inoculation of mice may be used as an adjunct to the fungus cultures [23].

In the past, blastomycosis has been treated with potassium iodide, radiation, excision and ethyl chloride spray. All treatments have been used with variable success. Schoenbach *et al.* [19], in 1951, reported good results with stilbamidine and more recently other investigators have used 2-hydroxystilbamidine with less toxic side effects [20-22,24]. One of the more common toxic manifestations of stilbamidine is trigeminal anesthesia. This may appear from one to five months after the first course of therapy. The drug can be hepatotoxic and renotoxic if it is not shielded from light during its preparation and administration. Full benefits from a course of treatment may not be achieved until two to three months after the final dose is administered [27].

The following case of primary laryngeal blastomycosis was recently seen at the Ohio Tuberculosis Hospital and illustrates several of the points discussed.

CASE REPORT

The patient was a forty-nine year old white man who had been in good health until early in 1953. At that time he noted the insidious onset of progressive hoarseness and a mild, persistent cough which was productive of 1 to 2 teaspoons of clear, foamy sputum daily. He consulted a private physician who treated him with several penicillin injections but the patient noted no improvement in his symptoms. Late in 1953 he noted the gradual onset of mild persistent dysphagia. In February, 1954, he was admitted to a county hospital where a laryngeal biopsy was reported as compatible with chronic tuberculous laryngitis. A sputum examination for acid-fast bacilli was negative at that time. Treatment with streptomycin and para-aminosalicylic acid was instituted, but after several months of therapy the patient reported no improvement in his symptoms. In March, 1955, because of occasional night sweats and intermittent blood streaking of his sputum, his medications were

changed to isoniazid and para-aminosalicylic acid. A sputum examination was again reported negative for acid-fast bacilli. The patient's hoarseness, cough and dysphagia persisted, and in the year prior to this admission there was a loss in weight of 20 pounds. Because of his failure to respond to antituberculous therapy he was referred to the Ohio Tuberculosis Hospital for further investigation of his illness.

A review of systems at the time of admission added no pertinent information. The patient denied all serious illnesses in the past. He stated that he had been a general farm hand for the past twelve to fifteen years, and had never been outside the state of Ohio.

Physical examination at the time of admission revealed the patient to be a thin white man appearing chronically ill but not in acute distress. The blood pressure was 130/80 mm. Hg; pulse, 85; respiration, 18; temperature, 98.6°F. The patient's hoarseness was so pronounced that he could only whisper. There was slight pharyngeal injection but no purulent exudate was noted. The epiglottis was thickened, edematous and fixed. A large ulceration was noted over the upper border of the epiglottis. Because of the marked edema of the epiglottis and surrounding structures, the vocal cords could not be visualized. The rest of the physical examination was within normal limits.

The red cell count was 5.26 per cu. mm., the hemoglobin was 16.8 gm. per cent and the white cells were 13,350 per cu. mm. with a differential count of 64 per cent neutrophils, 3 per cent eosinophils, 11 per cent monocytes and 22 per cent lymphocytes. The hematocrit was 52 per cent.

Skin tests revealed a P.P.D. No. 2 of 9 mm.; histoplasmin skin test of 11 mm.; and blastomycin skin test of 7 mm.

The serum albumin was 3.6 gm. per cent and the globulin was 2.4 gm. per cent. The electrophoretic pattern was normal, as were the blood urea nitrogen, cephalin flocculation test, bromsulphalein® excretion and alkaline phosphatase. Ten sputum cultures for fungi and six sputum cultures for acid-fast bacilli were reported negative.

X-rays of the chest taken on admission revealed minimal pleural thickening at the right apex. A barium study of the esophagus was normal. Laminagrams of the larynx revealed asymmetry of the glottis. The left vocal cord was not well outlined. These findings were interpreted as compatible with an infiltrating process in the area of the vocal cords.

The patient remained afebrile throughout his hospital course. Because of the previous biopsy diagnosis of tuberculous laryngitis, the antituberculous therapy was continued. A direct laryngoscopy was attempted but the vocal cords could not be visualized because of the pronounced edema of the epiglottis and surrounding structures. Biopsy specimens were obtained from the interarytenoid area, the false vocal

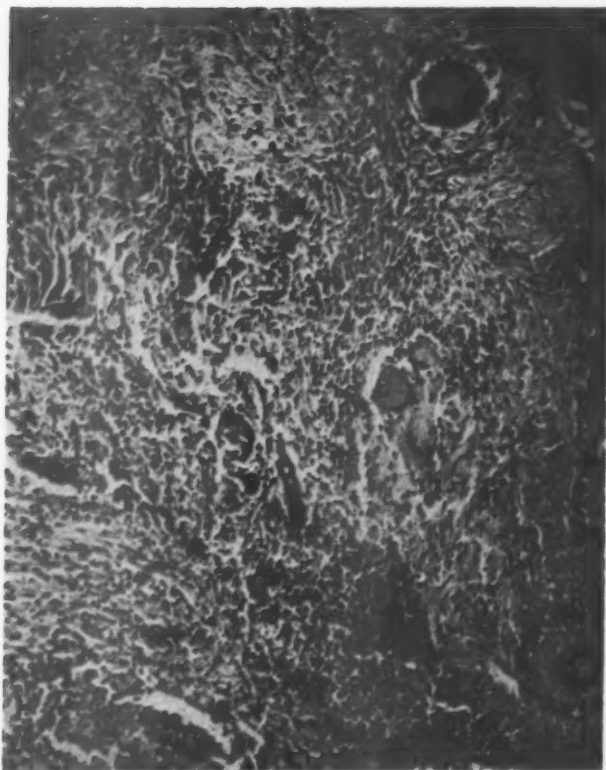


FIG. 1. The tissue reaction in the larynx consists of epithelioid cell tubercle formations with scarring, lymphocytic infiltration and Langhans' type giant cells. Hematoxylin and eosin, original magnification $\times 120$.

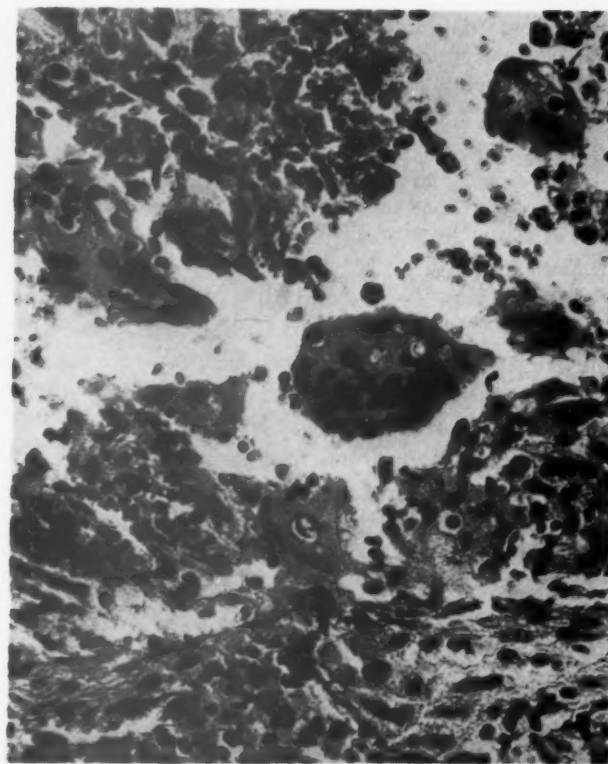


FIG. 2. Numerous blastomyces-like organisms are seen in the Langhans giant cells. Hemotoxylin and eosin, original magnification $\times 500$.

cords and the epiglottis. Microscopic examination of the biopsy specimens revealed tubercles without caseation, giant cells and a moderate number of yeast-like organisms which were identified morphologically as belonging to the blastomyces group of fungi. (Figs. 1, 2 and 3.)

When the diagnosis of laryngeal blastomycosis had been established, treatment was instituted with 225 mg. of 2-hydroxystilbamidine daily, administered intravenously, for thirty days. After the course of treatment had been completed the patient stated that his dysphagia had disappeared and that he no longer had a sense of fullness in his throat. There was no improvement in his hoarseness. Indirect laryngoscopy at that time revealed persistent edema of the epiglottis. The ulceration noted on admission had apparently healed. It was still difficult to visualize the true vocal cords. Only the anterior one-fourth of the left vocal cord could be seen and it appeared thickened and inflamed. Direct laryngoscopy was contemplated but the patient refused and insisted upon leaving the hospital.

The patient was seen three months after his discharge from the hospital. He had gained 10 pounds in weight and was asymptomatic except for his persistent hoarseness which had not improved. On examination the epiglottis was small and showed no evidence of



FIG. 3. Schiff-positive organisms are seen in another giant cell. Periodic acid-Schiff, original magnification $\times 500$.

inflammation, edema or ulceration. There was no stenosis or edema of the larynx. The vocal cords were thickened and movement was minimal when the patient attempted to phonate.

COMMENTS

Primary laryngeal blastomycosis is initially manifested by an upper respiratory infection which is usually associated with or closely followed by progressive hoarseness, cough with purulent sputum, occasional hemoptysis, weight loss, fatigue, dyspnea, dysphagia and a low grade fever. Examination of the hypopharynx reveals edema of the epiglottis and adjacent structures. The laryngeal surfaces are inflamed and covered with numerous, minute, grayish nodules among which are interspersed occasional yellow nodules. These represent small abscesses. Ulceration is common and the ulcerated areas are frequently covered with a gray membrane. Tubercle formation is not as prominent as in tuberculosis and, although caseation may occur, the centers of the tubercles are frequently composed of polymorphonuclear leukocytes, lymphocytes or both. Giant cells are often associated with the tubercles and the fungus is often found inside these cells. Blastomycosis differs from tuberculosis in its greater tendency to heal by fibrosis and absorption [9].

Because of the possible confusion with tuberculous laryngitis and carcinoma of the larynx, biopsy of the larynx is the most important single diagnostic procedure. Of the twelve previously reported patients, seven had tracheostomies and two had total laryngectomies before the diagnosis was established.

In reviewing the American literature it was difficult to establish the exact number of cases of primary laryngeal blastomycosis which have been diagnosed in this country. Several of the reports encountered failed to substantiate the clinical diagnosis with cultures of the organism or positive identification of the organism in tissue biopsies. In some reported cases there were definite pulmonary infiltrations; in these it was difficult to establish the primary site of the infection.

SUMMARY

A brief review of the literature of blastomycosis, with special reference to primary laryngeal involvement, is presented. The case presented in this paper is the thirteenth reported case of

primary laryngeal blastomycosis and the first to be treated with 2-hydroxystilbamidine.

Acknowledgments: We would like to express our gratitude to Dr. Philip C. Pratt for his invaluable aid in studying the pathologic specimens, and also to Dr. R. H. Browning for his helpful suggestions.

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Outbreak of Q Fever in an Army Installation in Italy*

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EARLY in 1956 at Camp Darby, Leghorn, Italy, there occurred an outbreak of fever of undetermined origin. The disease was char-



FIG. 1. Chest film taken on admission showing two rounded infiltrations, the typical "ground glass" opacities of Q fever. This eighteen year old soldier had been sick for four days complaining of sudden onset of myalgia, frontal headache, chills and fever and insomnia. Physical and laboratory findings were normal with the exception of a Q fever complement-fixation test positive in 1:80 titer.

acterized by sudden onset of varying high temperature, severe headache, generalized muscular aching, and almost complete absence of other symptoms. Ultimately this disease was positively diagnosed as Q fever, and the following report is a summary of the findings in forty-nine proved cases.

The typical course of the disease in this outbreak involved initial complaints of sudden onset of fever, general malaise, muscular aching and severe headache. The fever was notable because of its rapid changes: temperatures observed in the admission office to be normal or slightly elevated would frequently rise within the hour to 102°F. or even 104°F. when observed on the wards. Temperature spikes were common in the early evening, along with an extreme diaphoresis.

The symptom eliciting the most bitter complaint was headache. It was not uncommon for a patient to say after the first day that barring headache he felt perfectly well. This frontal or retroorbital headache was severe and unrelenting, and was aggravated by movement of the head or eyes.

Although cough was not a prominent complaint, and few patients had physical findings indicative of respiratory disease, most of them demonstrated an atypical pneumonitis (Fig. 1) that was discovered on routine chest films taken on admission. The number of patients with pulmonary infiltrations increased when repeat chest plates were taken after admission. With clinical response it was believed that there should be evidence of resolution in chest films; instead, most films showed a more generally diffuse area of pneumonitis. Resolution of the infiltrations radiographically did not occur in less than two to three weeks. This pulmonary involvement was noted in 77.5 per cent of our patients.

Complications included shock, disorientation, nausea and vomiting, pleuritic-type pain, dehydration and vertigo.

The possibility of Q fever must be considered in the differential diagnosis of any influenza-like disease. Unlike other rickettsial diseases, Q fever causes no rash and fails to produce cross-agglutinins with the proteus organisms in the Weil-Felix reaction. The positive diagnosis of Q

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fever depends on isolation of the causative organism, *Coxiella burnetii*, from animals inoculated with the patient's blood, or demonstration of a rising titer of complement-fixing or agglutination antibodies during the course of the disease or in early convalescence. The agglutination test is superior to the complement-fixation test in making an early diagnosis of the disease because the serum becomes positive more quickly. However, the complement-fixation test was used in this study since it was more practical for our laboratories to perform. In a number of our patients there was no demonstrable titer in the acute stage, but the convalescent serums became positive. Complement-fixing antibodies appeared during the second week of the disease and reached a peak about the end of the third week. Titers varied from 1:10 to 1:320.

Appropriate antibiotic therapy proved successful in treating these infections. Oxytetracycline (terramycin®) was the most effective of several antibiotics tried, and was used most extensively in our series. From 1 to 2 gm. was given daily in divided doses. Clinical response occurred in about forty-five hours, and the average length of treatment was 4.4 days. In a few instances, chlortetracycline (aureomycin®) was used, with nearly equivalent results except that clinical response was slightly less prompt. Penicillin did not seem to alter the course of the disease. Early in the series several patients were given penicillin and streptomycin but were switched to oxytetracycline when no response was noted. Apart from these antibiotics, no other therapy was employed except general supportive and symptomatic measures.

No relapses occurred with this therapy, and convalescence was about what could be expected in any influenza-like disease.

COMMENTS

The literature on many aspects of Q fever has been recently summarized in the comprehensive review by Wentworth [1]. The disease was first described in 1937 by Derrick [2], who observed an outbreak in Brisbane, Australia, and described the causative organism, a rickettsia now called *C. burnetii*. *C. burnetii* varies from the type organism, *Rickettsia prowazekii*, in that it is filtrable, more resistant to physical and chemical agents, produces no soluble antigens, does not produce agglutinins to proteus organisms, and does not produce a rash in patients.

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During and after World War II it became clear that Q fever was endemic in various parts of the world, especially in Italy, Switzerland, Germany, the Balkans, Panama and in California in the United States. It is of medical importance in endemic areas and owes its military significance to its high attack rate among troops stationed in these areas. Robbins and others [3] reported an attack rate of 20 to 30 per cent in troops stationed in certain areas of Italy during World War II.

A number of mammals, including common farm animals, serve as reservoirs of infection, but the usual mode of transmission to man is uncertain. Although ticks are known to be vectors of other rickettsial diseases, and although *C. burnetii* has been recovered from ticks, Q fever does not appear to be transmitted by tick bite. The organism has been recovered from the raw milk of cows and sheep, as well as the placentas and feces of these animals. In the Leghorn epidemic, neither tick nor milk transmission could be proved, and none of the patients had been in close association with animals.

Inhalation of infected dust, which appeared to be the usual mode of transmission in the northern California outbreak in 1951 [4], was the most likely cause of the Leghorn epidemic, since all the patients came from an area of the camp adjacent to farms harboring cattle and sheep. It is unlikely that person-to-person spread was responsible for many of our cases, since no infection occurred among the hospital personnel caring for these patients.

Ruling out the possibility of previous Q fever, any level of titer is said to be sufficient for diagnosis. Ormsbee [5] found in the titration of antibiotic effectiveness in experimental Q fever in embryonated eggs that oxytetracycline and chlortetracycline could prevent the appearance of positive titers for a period of days; and that with large dosages the level of titer could be kept lower than that of the controls. This antibiotic effect on titer by complement-fixation may account for the spread of titers noted in our series.

CONCLUSIONS AND SUMMARY

This report concerns the findings in forty-nine serologically proved cases of Q fever occurring in an outbreak at a U. S. Army installation in Italy during early 1956. The disease was characterized by varying high fever, severe headache, a lack of positive physical findings, and radiographic

evidence of an atypical pneumonitis which resolved only after two or three weeks.

Antibiotic therapy with oxytetracycline achieved good clinical response within two days; other antibiotics were less effective.

The disease appeared to be transmitted by inhalation of infected dust from animals on nearby farms.

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Observations on a Case of Primary Aldosteronism*

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DESOXYCORTICOSTERONE has been used in the therapy of adrenal insufficiency since its synthesis in 1937 by Steiger and Reichstein [1]. However, the amorphous fraction of adrenal cortical extracts was early shown to have a higher electrolyte activity than desoxycorticosterone. In 1953 three groups [2] working in collaboration isolated and crystallized the active steroid in the amorphous fraction. This same group later established its chemical structure and called the corticosterone, aldosterone [3].

In 1941 Ferrebee and associates [4] reported that large doses of desoxycorticosterone produced sodium retention, potassium loss, polydipsia, polyuria and intermittent paralysis in dogs. Other authors [5,6] have described similar, although milder, manifestations in human subjects given overdoses of the steroid.

In 1954 Conn [7] demonstrated excessive sodium-retaining corticoids, identified as aldosterone, in a patient and later reported correction of this abnormality by the removal of an adrenal cortical adenoma [8]. Shortly after this we observed a patient with this syndrome and have reported his cure [9]. Other case reports [10-14] have appeared in the literature since Conn's initial description. The following is a report of our second case with this syndrome.

CASE REPORT

V. W., a forty-three year old housewife was first seen in the White Memorial Clinic on February 20, 1955. She stated that she had been well prior to a hysterectomy for fibroids in 1951. After that she began to have spells of muscle weakness, notably involving the lower extremities but also the upper extremities.

She had had five severe spells which had started gradually, lasted for three to seven days, and subsided gradually. On four occasions the paresis was so severe that the patient had collapsed. During the past month the attacks had persisted for longer periods. There were no known precipitating factors.

The patient had had known hypertension for the past two years. She knew that prior to that time her blood pressure was low normal.

For one year she had been troubled with severe, poorly localized headaches which occurred about once a month and lasted one day. No aura was noticed. Nausea and vomiting developed during the headache and tended to relieve it. For one month she had had a constant dull aching pain in the anterior tibial, knee and thigh areas. This pain was most pronounced during episodes of muscle weakness. There were no other complaints.

The review of systems brought out the following other pertinent facts. She had not been very thirsty, but because of a slightly dry mouth she had drunk approximately 2 to 3 L. of water daily for the past eighteen months. Nocturia had gradually increased over the past year to four or five times nightly. She had also noticed mild pitting edema of the ankles for three or four months. There had been no muscle cramps or other symptoms suggesting tetany.

The patient's past history and family history were negative for hypertension or paralysis.

On physical examination the patient was found to be a normal appearing, well developed, white woman in apparent good health. There was nothing unusual about the body build or facial characteristics. The skin was free of acne and striae. The blood pressure was 170/100 mm. Hg in both arms (sitting). The pulse rate was 60 per minute. The heart was of normal size with good heart sounds and no murmurs. There was no detectable muscle weakness. Edema was not present. There were no reflex abnormalities at the

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initial examination. Chvostek's and Trousseau's signs were absent.

The initial laboratory findings are summarized in Table I. In addition, three electrocardiograms were consistent with the presence of hypokalemia, with a QT interval of 0.54 seconds at a rate of 54 per minute.

EXCRETION RATE MGM PER 24 HRS

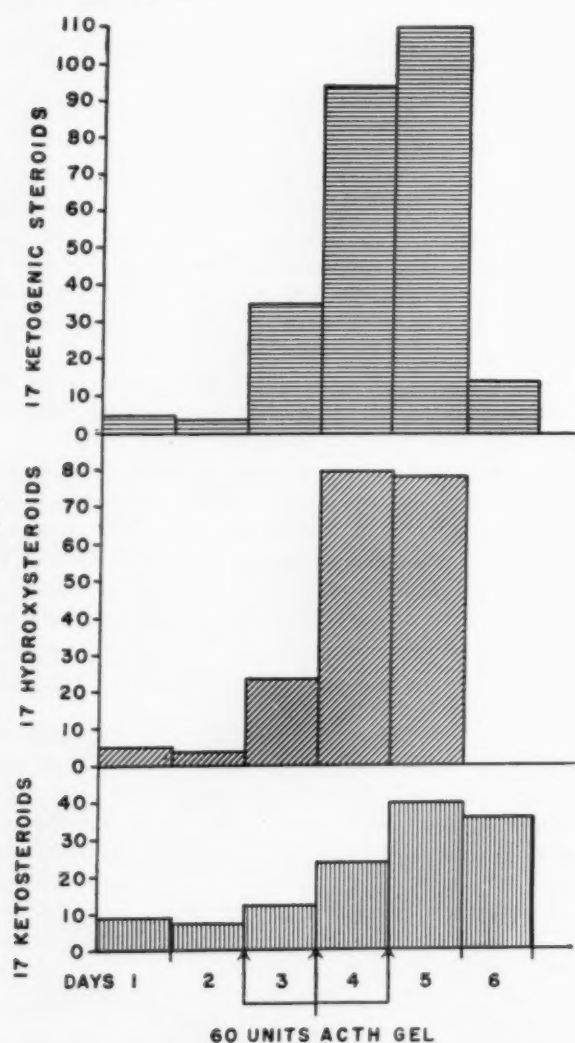


FIG. 1. Influence on twenty-four-hour output of 17-ketosteroids, 17-ketogenic steroids and 17-hydroxysteroids of adrenocorticotropin (gel), 60 units once daily.

The circulating eosinophil count dropped from 244 to 136 per cu. mm. four hours after administration of 25 units of adrenocorticotrophic hormone. There was no drop in blood pressure after the administration of 5 mg. of regitine.[®] The blood pressure dropped from 180/120 to 140/80 mm. Hg. after 5.5 gm. of sodium amytal[®] was given orally. A chest x-ray and an intravenous pyelogram were normal.

The patient was given supplemental potassium chloride in doses of 54 mEq./day. This tended to

relieve the muscle weakness and soreness for about one month on that dosage. However, these complaints persisted, although less severely, even with a dosage of potassium chloride of 150 mEq./day. This dose over a period of three months failed to sustain the serum potassium over 3.1 mEq./L.

TABLE I
INITIAL LABORATORY FINDINGS

Blood Values	
Hemoglobin (gm. %)	16
White blood cell count (per cu. mm.)	6,800
CO ₂ combining power (mEq./L.)	25
Serum potassium (mEq./L.)	2.1-3.1
Serum sodium (mEq./L.)	135-149
Serum calcium (mg. %)	9.5
Non-protein nitrogen (mg. %)	30
Fasting blood sugar (mg. %)	109

Urine Values

Urine protein negative	and pH neutral
Phenolsulphthalein	70% excreted in 2 hours
18 hour concentration test	specific gravity, 1.012 maximum
Uropepsin	20 units/hour (normal, 15-40 units/hour)

TABLE II
ADDITIONAL LABORATORY FINDINGS

Tests	Results
Alveolar pCO ₂ } simultaneously Arterial pH } obtained	39 and 37 mm. Hg (normal, 35-45 mm. Hg) 7.42 and 7.44 (normal, 7.35-7.45)
Extracellular sodium	2451 mEq. (normal, 1960 mEq.)
Intracellular sodium	590 mEq. (normal, 460 mEq.)
Exchangeable sodium	3041 mEq. (normal, 2420 mEq.)
Exchangeable sodium/Kg.	46.4 mEq./Kg. (normal, 35.7-41.6)
Biological decay time of radioactive sodium	40 days (normal, 8-14 days)
Exchangeable potassium	2084 mEq. (normal, 2820 mEq.)
Exchangeable potassium/Kg.	31.6 mEq./kg. (normal, 38.5-54.4)
Sweat sodium	17.8 mEq./L. (normal, 45 mEq./L.)
Bioassay of urinary sodium-retaining corticoids	
July 11, 1955	100 µg. equivalents of DCA/24 hr.
November 30, 1955	200 µg. equivalents of DCA/24 hr. (normal, 0-115 µg. equivalents of DCA)
Uropepsin excretion rate	79 units/hour 106 units/hour (normal, 15-40)

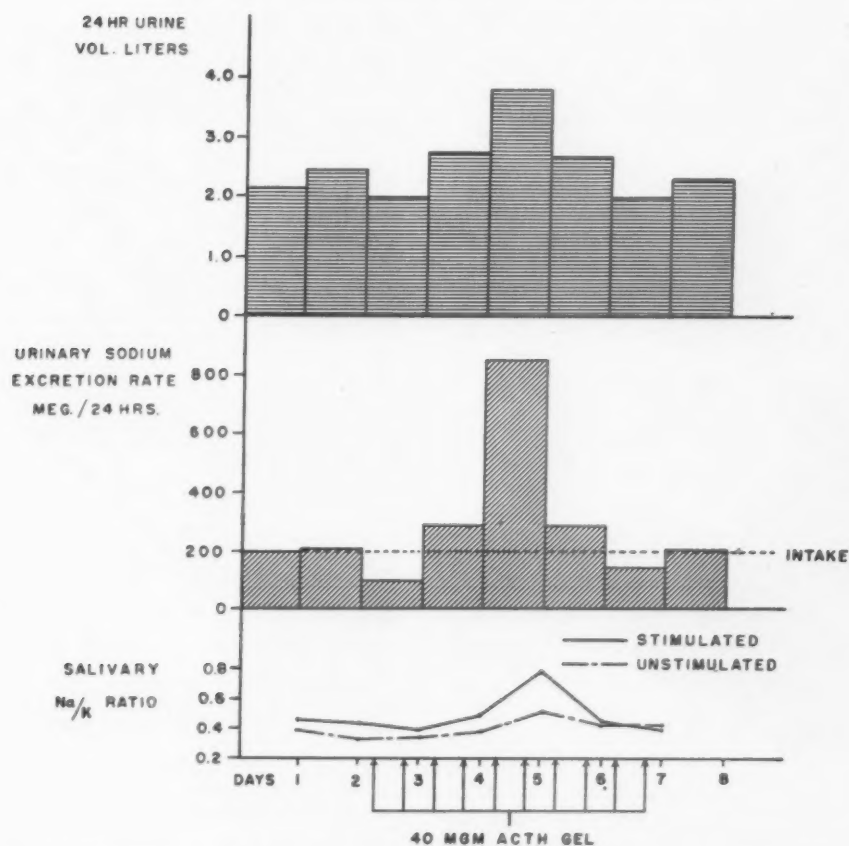


FIG. 2. Influence on the urine output, sodium excretion rate and salivary sodium:potassium ratio of adrenocorticotropin (gel), 40 mg. twice daily.

Further studies were instituted because of the clinical picture and the resistance to repletion of potassium. The results are listed in Table II.

The average sodium:potassium ratio in fourteen mid-morning saliva specimens was 0.21 (normal 0.5 to 1.5) in unstimulated saliva and 0.18 in saliva stimulated by the chewing of paraffin. The patient had difficulty producing the saliva without the aid of the paraffin, requiring as long as thirty minutes to obtain 15 ml.

The patient's exchangeable sodium was determined, using Na^{22} . Following the test dose an attempt was made to increase the rate of excretion of the radiosodium by giving the patient a normal diet plus an additional 200 mEq. of sodium chloride per day in divided doses. For the first three days after starting the extra sodium chloride she had severe headache, and pitting edema of the ankles developed. Over the ten-day period that the extra sodium was taken she gained eight pounds in weight. When the extra sodium was discontinued the edema subsided and the weight returned to normal by the third day. There was only an 11 per cent drop in the serum Na^{22} concentration in the ten-day period. Carbo-resin in doses of 8 gm. four times a day for seven days resulted in a further decrease of 87 per cent in the serum concentration of Na^{22} .

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The patient was next studied to evaluate the steroid response to adrenocorticotrophic hormone. The results of these studies are shown in Figure 1 (see Results).

The white blood cell alkaline phosphatase was studied by Dr. Jim Follette [15]. He reported that the values were 17 units before ACTH (normal 10 to 50 units), 83 units on the third day of ACTH administration, and 12 units twenty-four hours after discontinuing ACTH.

Conn observed that administration of ACTH to his patient resulted in two to three days of sodium retention followed by a sharp diuresis of sodium and chloride. Figure 2 shows the results of such a study in this patient (see Results).

The average daily urine volume when not influenced by ACTH was 2,200 ml. (range 1,560 to 3,240 ml.). The patient was able to reduce the urine volume by regulating fluid intake. Five urine specimens had pH values ranging from slightly acid to alkaline. There was no proteinuria. The specific gravity ranged from 1.003 to 1.010. The kidney had limited ability to concentrate the urine as evidenced by a maximum specific gravity of 1.012 after an eighteen-hour concentration test.

The first bioassay for mineralocorticoids in the urine (Table II) gave a value at the upper limits of

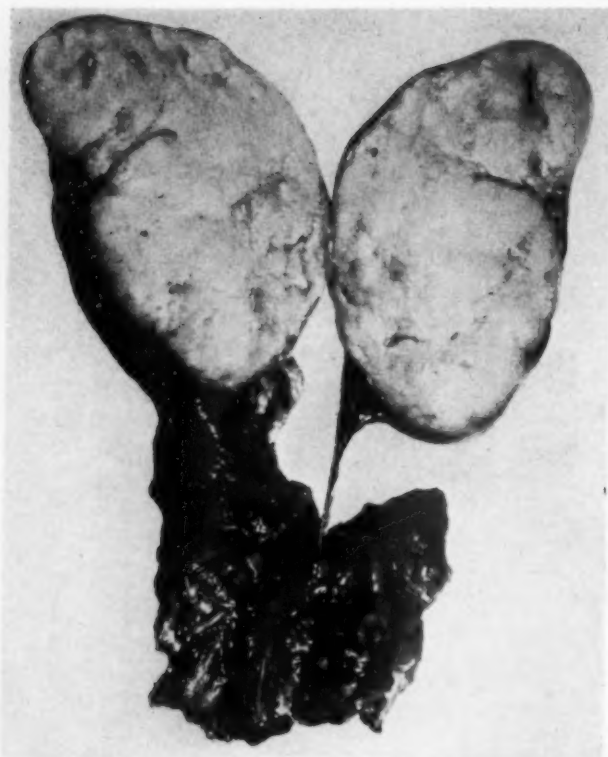


FIG. 3. Cross section of the adenoma showing the thin-walled capsule and homogenous surface; pictured as attached to the portion of the adrenal gland removed. Original magnification, $\times 1.5$.

normal. The second urine sample yielded values of twice the upper limits of normal. Although the mineralocorticoid assay was only slightly elevated, a condition of sodium retention and potassium depletion due to excess output of mineralocorticoids was suspected. Clinically the patient continued to have a dry mouth, a choking, tired feeling in the throat and neck, and weakness of thigh, calf and arm muscles moderately relieved by supplemental potassium chloride and exacerbated by its withdrawal. Accordingly, on November 30, 1955, the patient was explored by Dr. E. Boehme for an adrenal cortical tumor. Through an anterior approach both adrenal glands and kidneys and the adjacent area were examined manually. An adrenal cortical adenoma measuring 2 by 3 by 5 cm. was removed from its site adjacent to and below the left adrenal gland. The cut surface demonstrated a thin capsule surrounding a canary yellow, homogeneous tumor. (Fig. 3.) The cells were large, polyhedral, with clear cytoplasm, of one type throughout the tumor and were arranged in small groups separated by fibrous septums. The cell type and arrangement resembled the zona fasciculata. (Fig. 4.) No evidence of malignancy was found. A biopsy specimen of the left adrenal gland appeared normal, without evidence of narrowing of any of the three cortical zones. Sudan IV stain of the adrenal gland failed to reveal any difference in the amount of sudanophilic material in the three cortical zones.

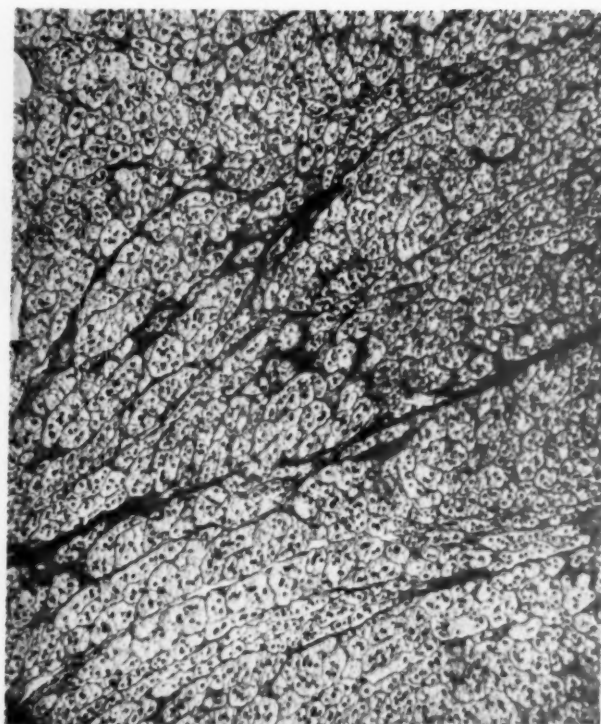


FIG. 4. Photomicrograph of the tumor demonstrating the cellular characteristics, which resemble those seen in the zona fasciculata. Original magnification, $\times 200$.

A biopsy of the kidney demonstrated some arteriolar sclerosis, but no areas of renal tubular degeneration were found.

The results of blood pressure recordings, potassium and sodium balance studies, and serum sodium and potassium concentrations during the immediate postoperative period are summarized in Figure 5.

The earliest subjective evidence that the condition had been corrected was on the third postoperative day when the patient noticed that she was able to sweat easily. The patient gradually regained her strength over the subsequent six weeks. She noticed easy fatigability for approximately six months. The blood pressure has remained about 130/85 mm. Hg.

METHODS

The sodium and potassium concentrations were determined by means of a Beckman Model DU flame photometer. Alveolar CO_2 determinations were made with an infra-red CO_2 analyzer, as described by Collier [16], at the time that the arterial samples were obtained anaerobically. The pH was determined immediately in a blood electrode of a Beckman Model G pH meter.

The exchangeable sodium was determined with sodium-22. One-hour and twenty-four-hour plasma samples were counted in a well-type scintillation counter after which the sodium concentration of the sample was determined by flame photometer. The extracellular content was calculated from the one-hour sample. The exchangeable sodium was calcu-

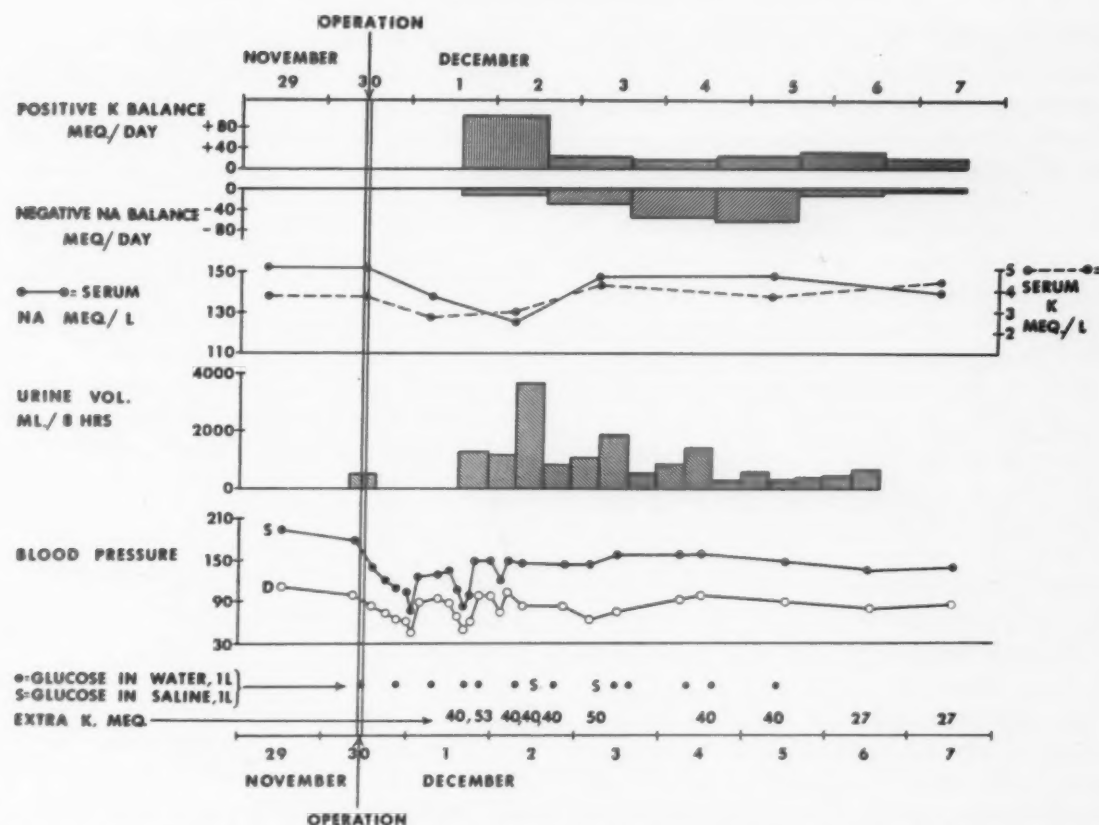


FIG. 5. Postoperative data. Graphic demonstration of sodium and potassium balance, serum sodium and potassium, urine volume, and blood pressures before and after removal of the adrenal cortical adenoma.

lated from the twenty-four-hour plasma specimen, correcting for the amount lost in the urine. The biological decay curve for sodium was determined from the plasma sodium-22 counting rates of samples obtained at seven to ten day intervals, correcting for any change in plasma sodium concentrations [17]. (The patient was taking about 200 mEq. per day of extra sodium chloride for both the pre- and post-operative biological decay time determinations.) The exchangeable potassium was determined by Dr. William Blahd using potassium-42. The thermal sweat specimen was collected with the patient in an atmosphere at 95°F. and 95 per cent humidity for one hour. Bioassays for mineralocorticoids were obtained through the courtesy of Dr. Jerome Conn. The method of Reddy [18] was used for the determination of the 17-hydroxysteroids, 17-ketogenic steroids were determined by the method of Norymberski [19], 17-ketosteroids were determined by the method of Dreker [20]. Urinary uropepsin determinations were made on timed specimens, collected under similar conditions in regard to time of day and relation to meals, and analyzed as described by West [21].

RESULTS

The results of the initial studies are summarized in Table I.

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Additional Laboratory Findings. The alveolar CO_2 , arterial pH and CO_2 combining power did not indicate the presence of metabolic alkalosis. (Table II.) The elevated exchangeable sodium, the prolonged biological decay time of sodium, the lowered sweat sodium concentration, and the lowered salivary sodium:potassium ratio suggested sodium retention. The low exchangeable potassium indicated that this sodium retention was in exchange for potassium. The bioassay of mineralocorticoids was, at first, within normal limits; but later was twice normal. The urinary uropepsin excretion rate was variable, about half of the results being normal, the others elevated. Figure 1 shows that the adrenals under base line conditions were excreting normal quantities of 17-ketogenic steroids, 17-hydroxysteroids and 17-ketosteroids. There was a marked increase in the excretion rate of these steroids with stimulation of 60 units of ACTH gel per day. Figure 2 shows that the administration of 40 units of ACTH gel daily to the patient for five days resulted in sodium retention on the first day of ACTH, then a diuresis of sodium and water most pronounced on the second, third

and fourth day of ACTH administration, with a peak output of 850 mEq. of sodium in 3,800 ml. of urine on the third day. A prior study demonstrated essentially the same results: early retention of sodium followed by a diuresis of

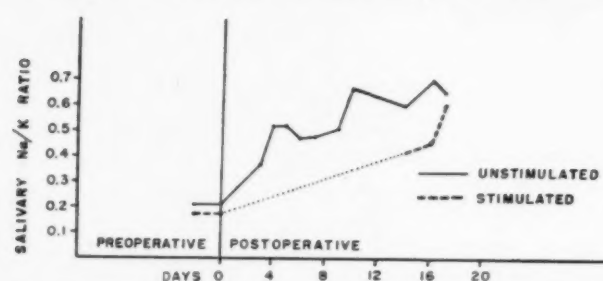


FIG. 6. Effect of the removal of the adrenal cortical adenoma on the salivary sodium:potassium ratio.

sodium, chloride and water on the third day of ACTH administration.

The salivary sodium:potassium ratio increased about three-fold on the day of maximal output of sodium, and then returned to the previous level. The stimulated salivary sodium:potassium ratio was consistently below the unstimulated saliva values. The urinary sodium:potassium ratio followed a similar pattern, with an increase from 1.10 to 1.85 on the third day.

Figure 5 illustrates some of the immediate postoperative events. About twelve hours after surgery the patient had a drop in blood pressure to 70/50 mm. Hg which had to be supported by continuous intravenous injection of vasoconstrictors for the next twelve hours. Oliguria was also noted, only 80 ml. of urine being excreted during the first thirty-six hours following surgery, in spite of infusion of 3 L. of 5 per cent glucose in water in that period. (Gastric suction was maintained for twenty-four hours, yielding 300 ml. in that time.) The addition of extra potassium (40 to 53 mEq.) to each of the next 4 L. of intravenously administered glucose in water seemed to correct this difficulty. Within two hours after starting the first liter of glucose and water containing 40 mEq. of potassium chloride, the blood pressure was maintained at about 150/100 mm. Hg without vasoconstrictors and the urine output was 1,200 ml. during the subsequent fifteen hours. The blood pressure leveled off at 130/80 mm. Hg. On the second and third days postoperatively the patient inadvertently received 150 mEq. of sodium chloride intravenously. A severe headache lasting three to five hours occurred after each of these venoclyses.

During the first seven days after operation the patient retained 210 mEq. of the 540 mEq. of potassium that she received and excreted 185 mEq. of sodium in excess of intake. The serum potassium reached 4.4 mEq./L. on the third

TABLE III
POSTOPERATIVE LABORATORY FINDINGS

Test	Six Weeks	Seven Months	One Year
Serum sodium (mEq./L.)	146	150
Serum potassium (mEq./L.)	5.1	4.8
CO ₂ combining power (mEq./L.)	28
Arterial pH	7.44
Alveolar CO ₂ (mm. Hg)	36
Thermal sweat sodium (mEq./L.)	45
Uropepsin excretion rate (units/hr.)	26	15
18-Hour urine concentration test, sp. gr. (maximum)	1.020	1.020	1.021
Extracellular sodium (mEq.)	2145	2266	2266
Intracellular sodium (mEq.)	546	357
Exchangeable sodium (mEq.)	2691	2623
Exchangeable sodium (mEq./kg.)	40.3	39.8
Biological decay time of radioactive sodium (days)	10
Exchangeable potassium (mEq.)	2337	2454
Exchangeable potassium (mEq./kg.)	34.9	38.0

day, dropped to 3.8 mEq./L. on the fifth day, but has been normal since.

Figure 6 demonstrates the gradual increase in the salivary sodium:potassium ratio from 0.21 before surgery to 0.64 by the tenth day after surgery.

Table III gives the postoperative laboratory findings. The CO₂ combining power, serum sodium, serum potassium, arterial pH and alveolar CO₂ were all within normal limits. The kidneys showed slight improvement so that the maximum specific gravity after an eighteen-hour concentration test reached 1.020. There has been no further significant improvement in the twelve months that have elapsed since surgery. The extracellular sodium decreased from 2451 mEq. to 2145 mEq., and the intracellular sodium decreased from 590 mEq. to 546 mEq., giving a total exchangeable sodium less by 350 mEq. The biological decay time of sodium was ten days, which shows a marked decrease from the preoperative value. The exchangeable potassium showed an increase of 370 mEq. (The body weight was the same for the determinations before and after surgery.)

COMMENTS

Aldosterone has been reported [22] to be 120 times as potent as desoxycorticosterone in influencing sodium and potassium metabolism.

Until the reports of Conn [7,8] no syndrome in man primarily due to an excess of mineralocorticoids, aldosterone in particular had been described. The clinical features of his case consisted of intermittent tetany, paresthesias, periodic severe muscular weakness and paralysis, polyuria and polydipsia, hypertension, not accompanied by edema. The laboratory findings were characterized by hypokalemia, hypernatremia, alkalosis, excessive excretion of sodium-retaining corticoids, and a renal tubular defect in water reabsorption. The excretion of 17-ketosteroids and 17-hydroxysteroids was normal.

An elevated excretion rate of aldosterone has also been found to be associated with other disease states such as essential hypertension [23], postoperative state [24], congenital adrenogenital syndrome [25], and particularly those disorders associated with edema, such as lipemic nephrosis [26,27], congestive heart failure [28], toxemia of pregnancy [29,30] and hepatic cirrhosis [30-33]. Luetscher [28] has demonstrated an increased excretion rate in normal persons who are maintained on less than 11 mEq. of sodium per day. More recently an increased excretion rate of aldosterone has been found to be related to the paralytic episodes in familial periodic paralysis [34] and to periodic paralysis associated with hyperthyroidism [35].

The mechanism controlling mineralocorticoid secretion has not been completely elucidated. Rosenfeld [36] has reported that a low sodium and a high potassium concentration in adrenal gland perfusate results in an increase in aldosterone output and that ACTH produces a slight increase in the output of aldosterone. Bartter [37] and Muller [38] have shown that the extracellular volume exerts some control on the aldosterone secretion. In general, it now appears that certain electrolytes [36,39,40], the extracellular volume [37] and, to a much lesser extent, ACTH control adrenal secretion of this hormone [36,41,42].

The disease entity named "primary aldosteronism" by Conn is most commonly caused by a benign adrenal cortical adenoma. Since his original report, seven [9-12,14] other cases have been recorded as cured by removal of an adrenal cortical adenoma; one patient [13] was too ill for surgery. Foye [43] has reported a patient with an adrenal cortical carcinoma, which produced solely mineralocorticoid effect, who was temporarily relieved by removal of the carcinoma. Spaulding [44] has presented a

patient with hypokalemia, hypochloremia and metabolic alkalosis apparently caused by an oat cell type bronchogenic carcinoma with metastases in the adrenal gland which was secreting predominantly a mineralocorticoid-like substance apparently different from aldosterone.

The case presented here was characterized by frequent headaches, hypertension, periodic muscle weakness, moderate polyuria and polydipsia, and hypopotassemia; but it differed from the other reported cases in some respects.

From observations on this case and that which was reported by Chalmers [12], it would appear that metabolic alkalosis is not necessarily present in all cases. Our patient had a normal pH, normal alveolar CO₂ and normal CO₂ combining power. We were unable to elicit any evidence of tetany or muscle cramps. The pains in the legs seemed to be entirely related to the overworking of some muscle groups as a result of weakened thigh muscles.

Under the influence of aldosterone the secretory body cells retain sodium and excrete potassium in exchange. This results in a decreased thermal sweat sodium, a decreased salivary sodium:potassium ratio and a higher renal threshold for sodium. Consequently there is an increased exchangeable sodium and a lowered exchangeable potassium. Metabolic studies in other cases [10,12] seem to indicate that there is also a total body deficit of chloride. The serum sodium may be normal or elevated, as borne out in both of our cases. Serum values, of course, do not necessarily reflect a total body deficit or excess.

The exchangeable sodium and potassium determinations and the postoperative balance studies confirmed the presence of a total body excess of sodium of about 350 mEq. and deficit of about 350 mEq. of potassium. Chalmers has reported similar observations in his case. Some of this extra sodium can be forced out by ACTH, cortisone or high doses of potassium [7,10,12].

The increase in the exchangeable sodium is less dramatic than the prolonged decay time for sodium as measured by sodium-22. Threefoot [17] has shown that the biological decay time is prolonged in congestive failure, nephrosis and in normal subjects on a low sodium intake. Extra sodium should shorten the decay time by 50 per cent or more in a normal patient. Extra sodium failed to shorten significantly the decay time in this patient until after the tumor was removed.

Not only is it difficult to remove the extra sodium but, as pointed out by Conn [7], it is difficult to achieve potassium repletion. Studies so far show that from 100 to 600 mEq. of potassium daily may be required to replenish and maintain body stores.

In the case presented, adrenocorticotropin increased the sodium:potassium ratio in both the saliva and urine temporarily. Normally, the sodium:potassium ratio increases two to three-fold upon the stimulation of chewing. However, this patient had no significant change with such stimulation. The normal range for sodium:potassium ratio is quite wide [45]. It is not unusual to find normal values below those of this patient. However, we have not observed any normal subjects to have such low figures which did not increase on stimulation. If the salivary sodium:potassium ratio is to be used as a screening test for this condition it seems to us that both an unstimulated and a stimulated saliva specimen should be analyzed. Further study will be needed to verify this since postoperatively, there was no noticeable increase in salivary sodium:potassium ratio on stimulation: that is, both the sodium and potassium values increased proportionately on chewing.

Hypertension in these cases could well be related to the increased total body sodium. Tobian [46] has reported that the aortas of patients with hypertension have a higher than normal sodium content. Patients with essential hypertension have been found to have a slightly higher urine output of aldosterone [23]. These findings all seem to indicate a definite relationship between the high body sodium, hypertension and aldosterone.

Frequent headache was a distressing symptom in the two patients we have observed. These headaches occurred spontaneously but in the present case could be precipitated by the administration (orally or intravenously) of sodium chloride.

Mild pitting edema was also noted intermittently by this patient. Weight gain and edema were observed particularly during the week of ingestion of extra sodium chloride. These observations suggest that the extracellular volume can be increased enough to produce edema in primary aldosteronism by giving extra sodium chloride. In this respect this case resembles the case of Mach [47]. The work of Jeanneret *et al.* [48] shows that mineralocorticoid activity seems to affect tubular sodium reabsorp-

tion, with related potassium loss. Chloride retention is a consequence of sodium retention, and both sodium and chloride retention seems to be necessary for water retention. One case [12] has been reported showing that an excess of aldosterone is associated with a deficit of total body chloride. This suggests that the polyuria is due to the inability of the renal tubules to retain chloride, the polydipsia being secondary to the diuresis. The urine output of 3 L. per day can be decreased to less than 1,500 ml. per day by voluntary restriction of fluid, as evidenced in this case and one other [10]. Foye [43] has suggested that the polyuria may be secondary to a hyponatremia-produced polydipsia.

In this condition the twenty-four hour output of mineralocorticoid may be within normal limits or only slightly elevated, as noted in this case and as reported by Chalmers [12]. This may be explained by a constant output of aldosterone from the adenoma which depresses aldosterone secretion from the adrenal cortex, either directly by the hormone itself or indirectly through the lowering of the serum potassium [49]. Also, only small quantities (0.4 to 4.3 per cent) of the administered hormone can be recovered from the urine [39]. The excretion rate of 17-ketosteroids, 17-hydroxysteroids and 17-ketogenic steroids is within normal limits, and there is no change in body characteristics as in Cushing's syndrome. In our first case we reported that the urinary uropepsin excretion rate was increased. The uropepsin excretion rate was found to be increased only about half of the time in this case. The adrenal glands seemed to respond to pituitary stimulation normally, as evidenced by a drop in the circulating eosinophils and by an increase in output of 17-ketogenic steroids, 17-hydroxysteroids, and 17-ketosteroid when ACTH was given.

Valentine and co-workers [15] have demonstrated that the leukocyte alkaline phosphatase level is related to pituitary-adrenal activity. In view of the normal base line values and normal response to ACTH stimulation in the present instance and in our first case, it would seem that aldosterone has essentially no effect on the leukocyte alkaline phosphatase level.

After the operation this patient had a drop in blood pressure which required the use of vasoconstrictors. The oliguria was not corrected by infusion of water. Since there was a minimum of blood loss at the time of surgery, it seemed most likely that the patient had a lowered extra-

cellular volume with a smaller plasma volume as the cause of shock. Administration of saline solution under those conditions should correct the low blood pressure. However, the exchangeable studies showed a total body excess of sodium and a deficit of potassium. With this in mind, it was believed that the course to follow should be to supply extra potassium in as large a dose as tolerated while monitoring the electrocardiograph for signs of overdosage. The extra potassium should allow the sodium to become available for expansion of the extracellular space and thus correct the hypotension and oliguria. The response to potassium chloride was so dramatic that we believe this to be the case. The stress of the operation, by stimulating the pituitary-adrenal axis, might result in some oliguria for a few days after surgery, followed by a diuresis of water and sodium. However, we would not expect such a marked response.

The anterior approach was selected for exploration so that both adrenal areas could be examined, in view of the extremely small adenoma (1 cm. in diameter) found in our first case (see also [17]).

Large doses of potassium ion seem to be well tolerated and are mandatory in some cases of primary aldosteronism after removal of the adenoma. No mention has been made of this problem in the other cases reported. Preoperative preparation with ACTH and potassium chloride for about three days would thus seem advisable considering the known influence of these substances on the total body stores of sodium and potassium in this disease.

SUMMARY

Another case of primary aldosteronism is recorded. This patient differs from others reported in that there was no chemical evidence of extracellular alkalosis and the excretion of mineralocorticoids in the urine was normal or only slightly elevated. The biological decay time of radioactive sodium was forty days before surgery and ten days after removal of the adenoma, both tests being performed with high sodium ingestion.

High intake of extra sodium chloride produced edema and headaches. Headache is considered to be a presenting complaint in these patients along with hypertension, spells of muscle weakness, polydipsia and polyuria.

The symptoms and the hypertension and

electrolyte disturbances were relieved by removal of a benign adrenal cortical adenoma.

It is suggested that a patient with primary aldosteronism should be given adrenocorticotropin and supplemental potassium chloride for about three to five days preoperatively to remove some of the extra sodium and to correct some of the potassium deficit.

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ENOVID*

BRAND OF NORETHYNODREL WITH ETHYNYLESTRADIOL 3-METHYL ETHER

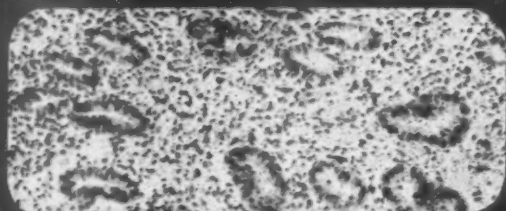
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Enovid is Searle's new, orally effective agent designed to provide specific control of menstrual disorders.

Enovid contains norethynodrel, a new synthetic steroid with strong progestational and lesser estrogenic activity. The estrogenic effect, enhanced by the addition of ethynylestradiol 3-methyl ether, prevents spotting or breakthrough bleeding in most patients in whom it would otherwise occur.

Like the normal endocrine action of the corpus luteum, Enovid maintains the integrity of the endometrium during administration of the drug. Moreover, as occurs on withdrawal of the natural hormone, the withdrawal of Enovid results in the flow characteristic of menstruation. Also, as does the natural hormone, Enovid controls the gonadotropic functions of the anterior pituitary glands.

This specific control of the menstrual cycle permits effective treatment of both excessive and inadequate endometrial activity and provides the physician with a dependable agent for treating such disorders as amenorrhea, dysmenorrhea, menorrhagia, metrorrhagia and premenstrual tension.



Pretreatment biopsy from patient with anovulatory menometrorrhagia.
Interpretation: Proliferative endometrium.



Post-treatment biopsy on day 25 after 10 mg. of Enovid daily from day 5 to day 20.
Interpretation: Late secretory endometrium with pseudo-decidual stromal development.

Biopsy photomicrographs courtesy of Anna L. Southam, M.D., New York, N.Y.

INDICATIONS AND DOSAGE GUIDE FOR ENOVID		
DISORDER	FIRST CYCLE	SECOND AND THIRD CONSECUTIVE CYCLES
Menorrhagia	One or two 10-mg. tablets daily to day 25 of the cycle.	One 10-mg. tablet daily from day 5 to day 25*
Metrorrhagia	One or two 10-mg. tablets daily to day 25 (or for 10 days to establish cycle)	same as above
Amenorrhea (primary or secondary)	One 10-mg. tablet daily for 20 days to establish cycle	same as above
Oligomenorrhea	One 10-mg. tablet daily from day 5 to day 25*	same as above
Premenstrual Tension	One 10-mg. tablet daily from day 5 to day 25*	same as above
Dysmenorrhea	One 10-mg. tablet daily from day 5 to day 25	One 10-mg. tablet daily from day 5 to day 25
Inadequate Luteal Phase	One 10-mg. tablet daily from day 15 to day 25	One 10-mg. tablet daily from day 15 to day 25

*The administration of Enovid prior to day 15 may interfere with ovulation; if anovulatory cycles are not desired, one 10-mg. tablet of Enovid should be administered daily from day 15 to day 25.

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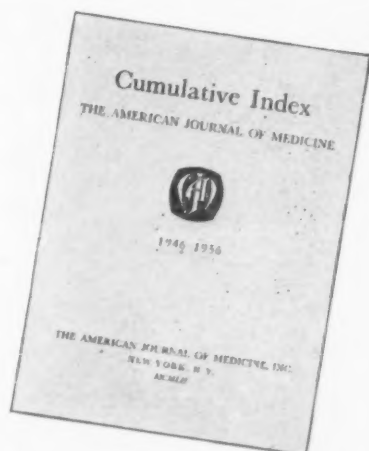
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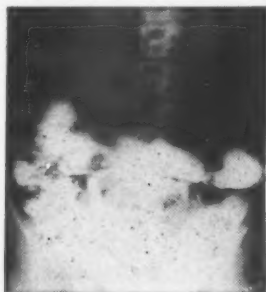
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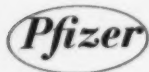
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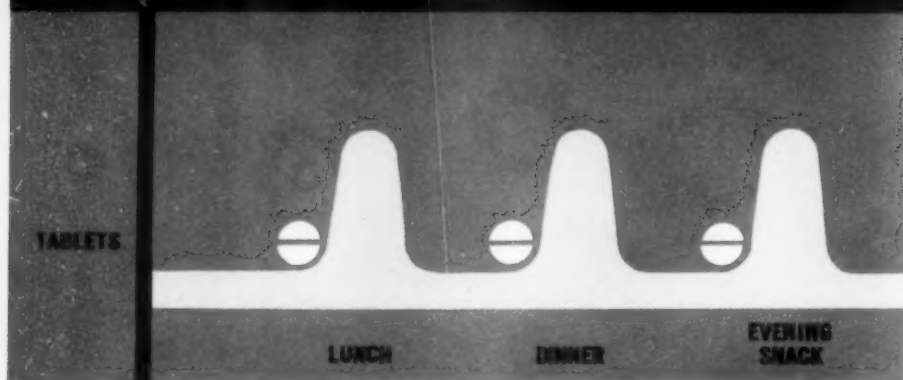
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1. Eisfelder, H.W.: *Am Pract. & Dig. Treat.* 5:778 (Oct. 1954)

2. Freed, S.C.: *G.P.* 7:63 (1953)

3. Sherman, R.J.: *Medical Times*, 82:107 (Feb. 1954)

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1. Bendig, A.: New York State J. M. 66:2523, 1956. 2. La Barbera, J. F.: Med. Rec. and Ann. 50:242, 1956. 3. Gilchrist, A. R.: Brit. M. J. No. II:1011, 1956.

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*REFERENCE: Zoll, P. M. et al: Termination of Ventricular Fibrillation in Man by Externally Applied Electric Countershock. New England Journal of Medicine — Vol. 254 — No. 16 — April 19, 1956.



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None	16%	22%	13%	19%
Few	46%	48%	50%	57%
Same	38%	38%	38%	24%
Complications:				
Hemorrhage	5%	7%	19%	9.5%
Perforation	0%	4%	0%	0%
Obstruction	0%	4%	0%	0%
Surgery needed	3%	4%	6%	0%
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1. After Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer, *Am. J. Digest. Dis.* 1:301 (July) 1956.

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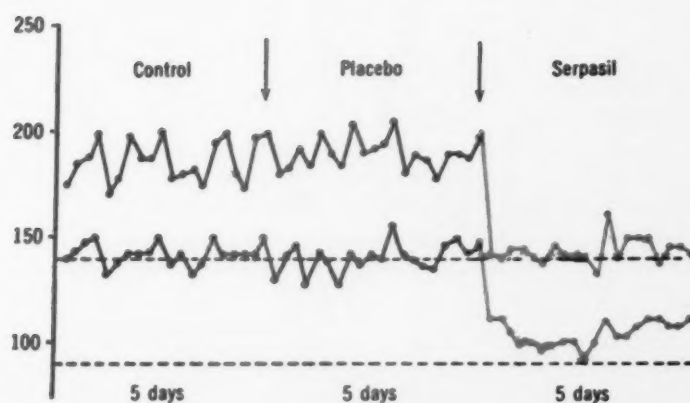
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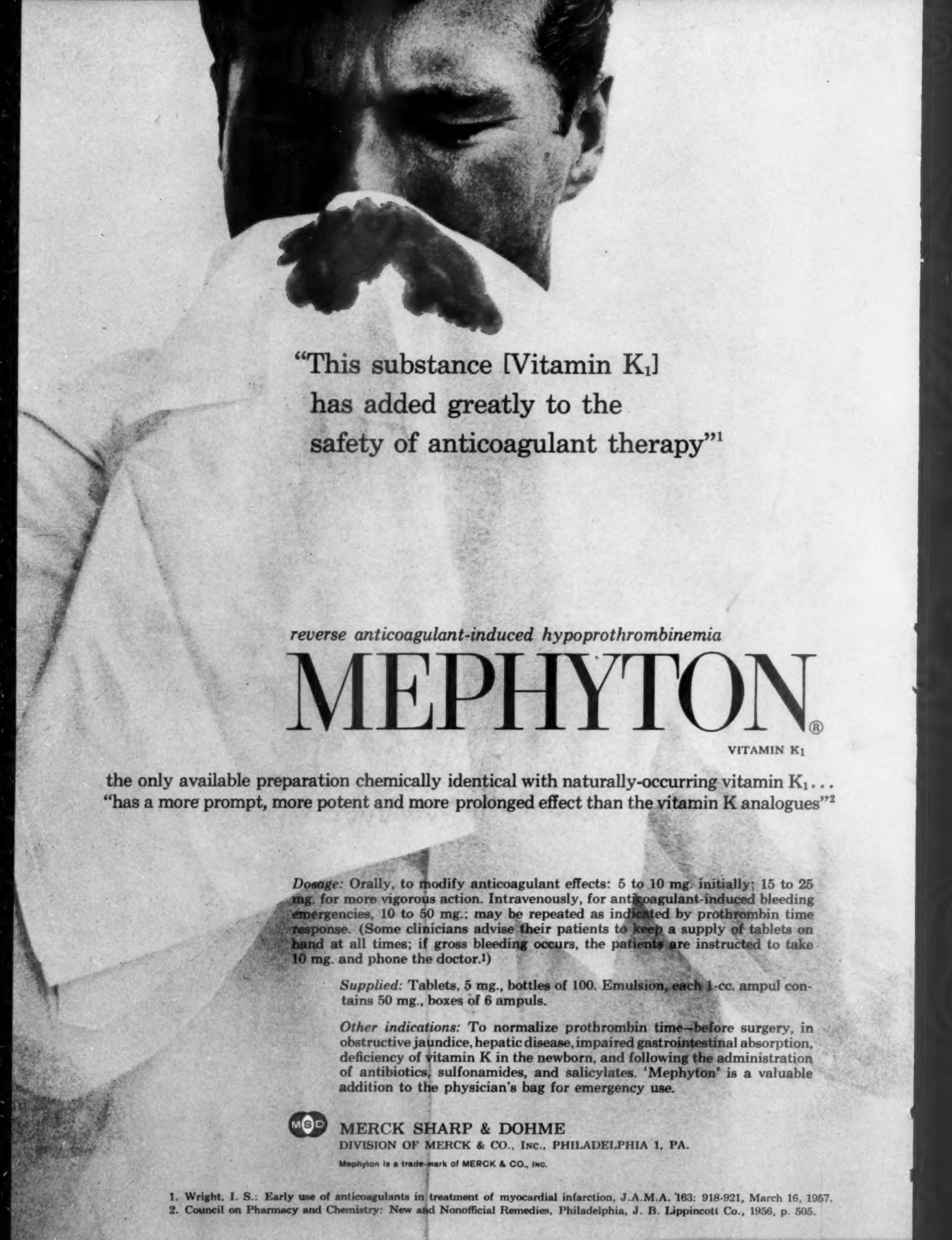
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1. Wright, I. S.: Early use of anticoagulants in treatment of myocardial infarction, J.A.M.A. 163: 918-921, March 16, 1957.
2. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.



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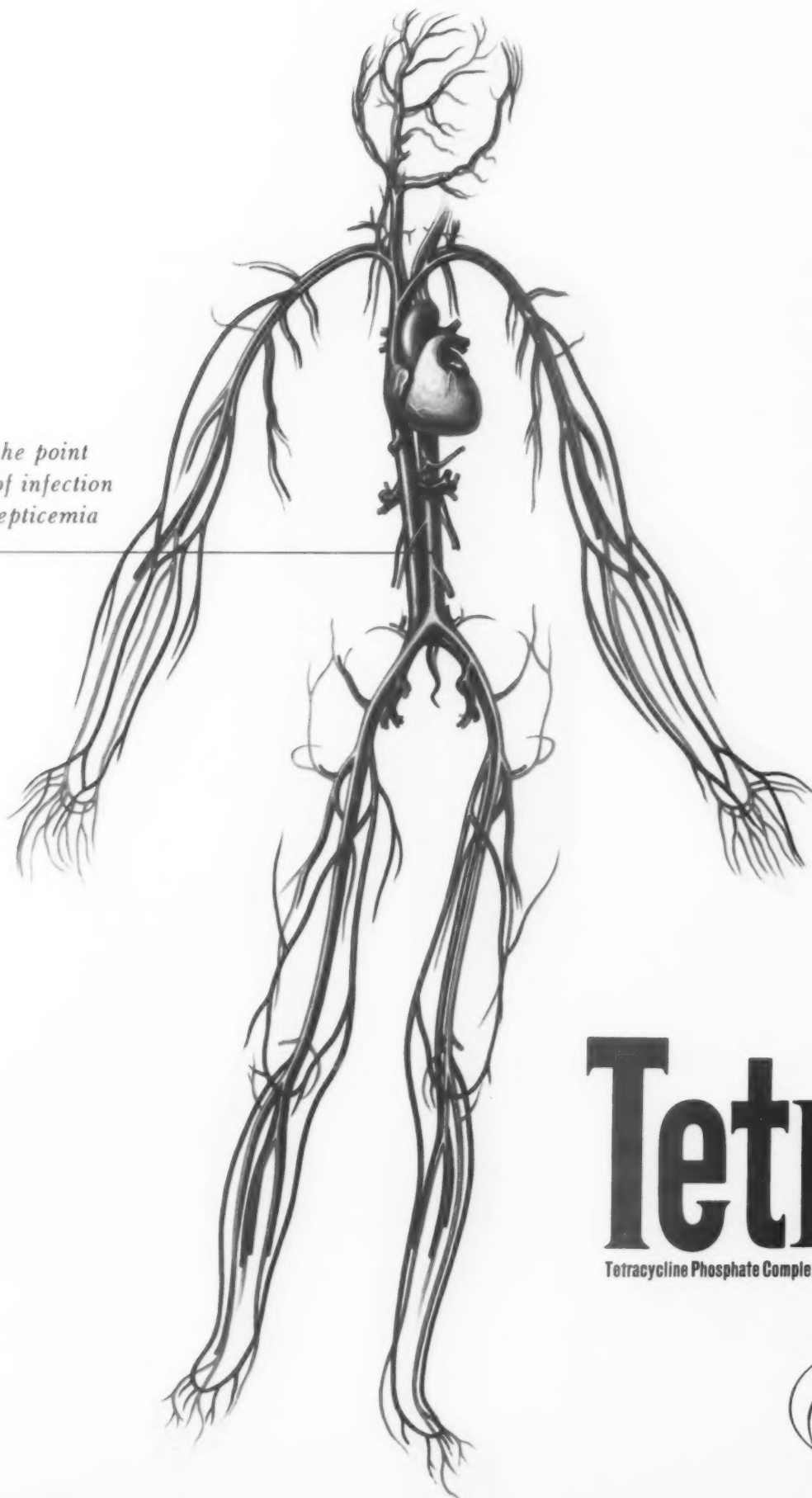
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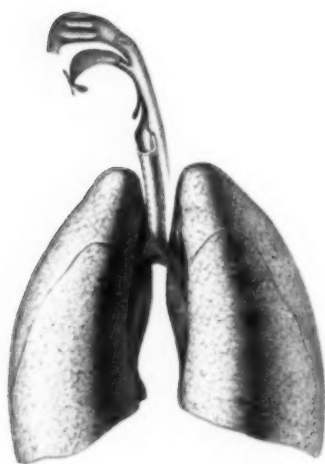
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Q. How does Marsilid act?

A. Marsilid restores a feeling of well-being and promotes an increase in appetite, weight and vitality. It restores depleted nervous energy and stimulates appetite and weight gain in chronic debilitating disorders.

Q. How soon is the effect of Marsilid apparent?

A. Marsilid is a relatively slow-acting drug; even in mild depression results may not be evident for a week or two. In chronically depressed or regressed psychotics, results may be apparent only after a month or more.

Q. How does Marsilid compare with shock treatment?

A. Marsilid usually obviates the need for shock treatment. The drug has repeatedly been effective in patients who had not responded to shock therapy (both insulin and electroshock).

Q. What is the dosage of Marsilid?

A. *Like all potent drugs, Marsilid requires individual dosage adjust-*

*T. R. Robie, paper read at First Marsilid Symposium, New York City, November 29, 1957.

ment for best results. Since Marsilid has a cumulative action, the dosage should be reduced after improvement is evident. *Ambulatory Patients* (mild depression): 50 mg daily—given in divided doses or as a single dose—followed by a gradual reduction to a lower maintenance dose until discontinuation of therapy becomes feasible. *Hospitalized Patients* (depressed and regressed psychotics): 50 mg t.i.d. until improvement is evident (in severe psychoses several months of treatment may be necessary before patients improve). Then reduce to lowest level at which improvement can be maintained. If Marsilid, or Marsilid with dextro-amphetamine, does not produce improvement, the addition of 1 mg of reserpine daily may result in a favorable response.

Q. What precautions should be taken with Marsilid?

A. While excessive doses of Marsilid may cause side effects, these reactions are usually reversible upon reduction of dosage or cessation of therapy. Vitamin B₆ (pyridoxine hydrochloride) frequently obviates or alleviates side reactions due to Marsilid. Marsilid should be used cautiously, if at all, in overactive, overstimulated or agitated patients because it may cause excessive stimulation; it is primarily recommended for depressed patients. Marsilid is probably contraindicated in patients with impaired liver function or with a history of previous liver disease; therapy should be interrupted promptly if jaundice appears. In patients with impaired kidney function, Marsilid should be used cautiously to prevent accumulation. Marsilid should not be used in epileptic patients.

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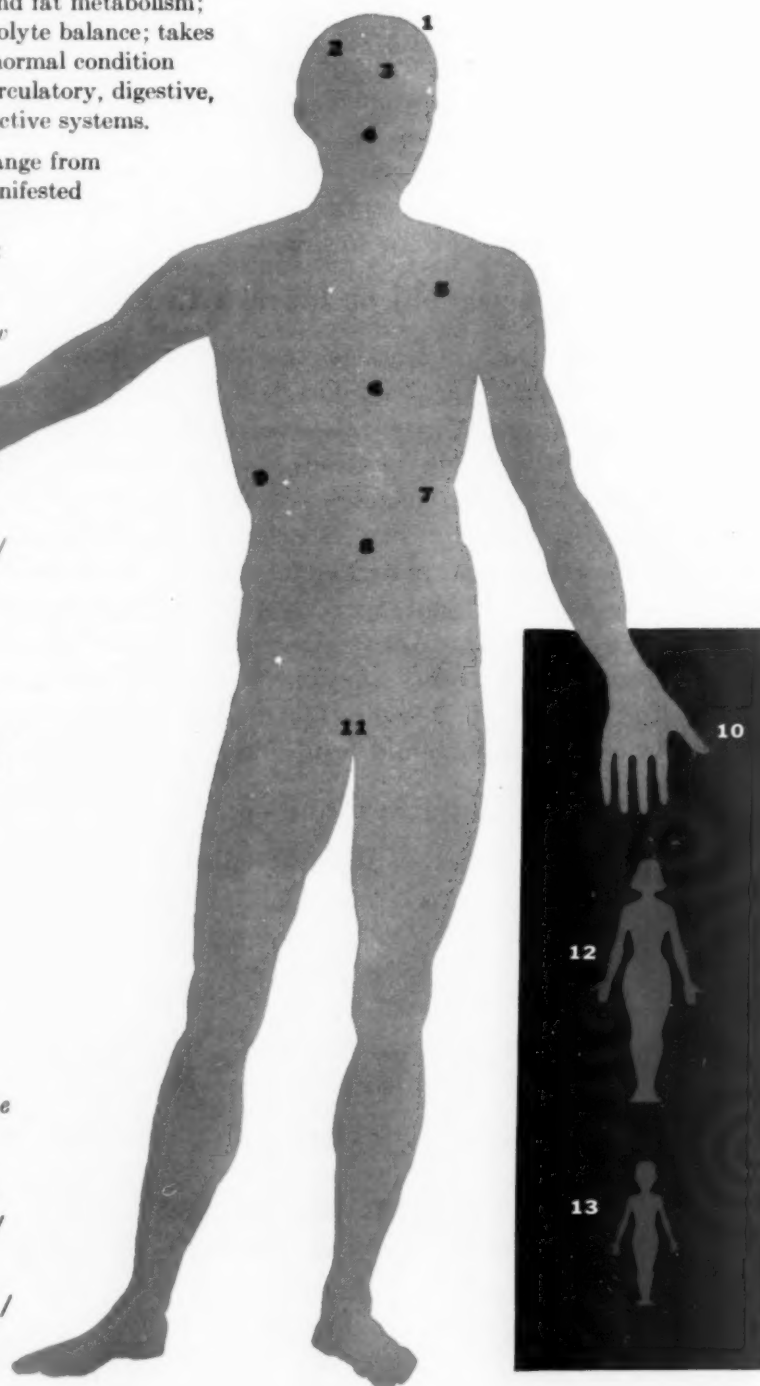
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a single syndrome with a host of symptoms

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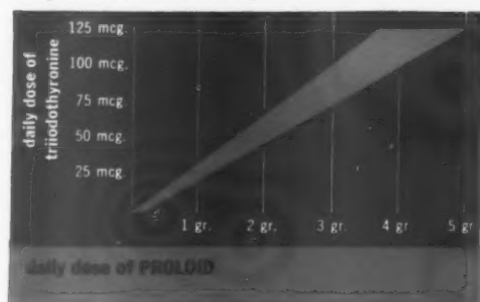
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- 1** Low BMR / Cold extremities / Elevated serum cholesterol / Slow pulse rate / Lack of energy / Sensitivity to cold / Overweight
- 2** Dry, falling hair
- 3** Somnolence / Chronic fatigue / Failing memory / Inability to concentrate / Delayed reflexes / Chronic headache / Irritability / Frank psychotics / Paresthesia
- 4** Chronic colds
- 5** Dry, coarse skin
- 6** Anemia
- 7** Sodium and water retention / Nonpitting edema / Diminished diuresis / Albuminuria
- 8** Achlorhydria / Flatulence / Constipation
- 9** Flabby muscles / Backache / Arthralgia / Myalgia
- 10** Brittle nails
- 11** Decreased libido / Infertility / Impotence
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Source—Hyman, M.: Some Aspects of Psychiatry in General Practice, GP 16:83 (Oct.) 1957.

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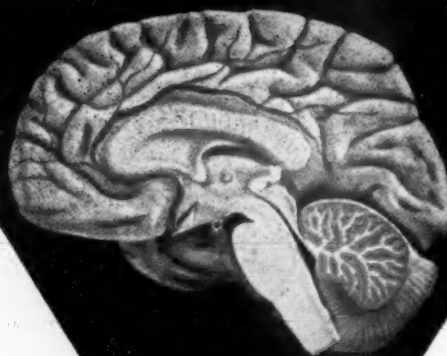
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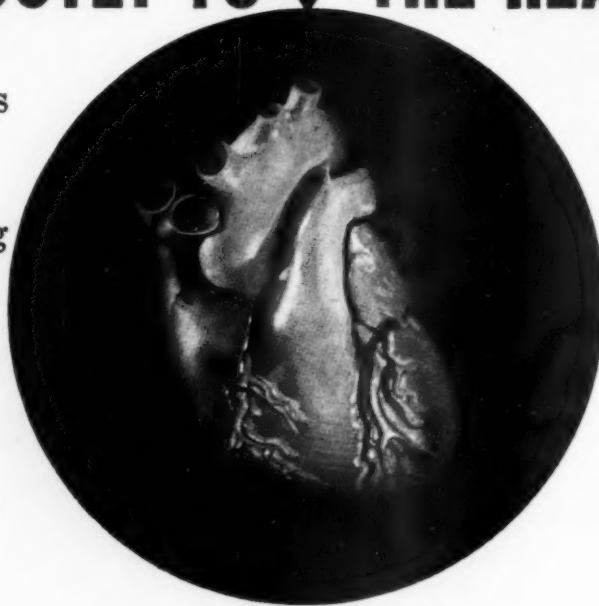
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